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(54) Title: MODULATORS OF PROTEIN TYROSINE PHOSPHATASES (PTPASES)

(57) Abstract

The present invention provides novel compounds, novel compositions, methods of their use, and methods of their manufacture, where such compounds are pharmacologically useful inhibitors of Protein Tyrosine Phosphatases (PTPase's) such as PTP1B, CD45, SHP-1, SHP-2, PTPα, LAR and HePTP or the like. The compounds are useful in the treatment of type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance, obesity, immune dysfunctions including autoimmunity diseases with dysfunctions of the coagulation system, allergic diseases including asthma, osteoporosis, proliferative disorders including cancer and psoriasis, diseases with decreased or increased synthesis or effects of growth hormone, diseases with decreased or increased synthesis of hormones or cytokines that regulate the release of/or response to growth hormone, diseases of the brain including Alzheimer's disease and schizophrenia, and infectious diseases.

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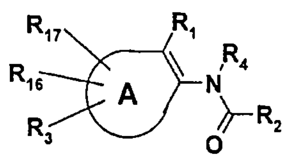
Modulators of Protein Tyrosine Phosphatases (PTPases)

FIELD OF THE INVENTION

The present invention relates to novel compounds, to methods for their preparation, to compositions comprising the compounds, to the use of these compounds as medicaments and their use in therapy, where such compounds of Formula 1 are pharmacologically useful inhibitors of Protein Tyrosine Phosphatases (PTPases) such as PTP1B, CD45, SHP-1, SHP-2, PTPα, LAR and HePTP or the like,



Formula 1

wherein A, R_1, R_2, R_3, R_4, R_{16} and R_{17} are defined more fully below.

It has been found that PTPases plays a major role in the intracellular modulation and regulation of fundamental cellular signalling mechanisms involved in metabolism, growth, proliferation and differentiation (Flint et al., The EMBO J. 12:1937-46 (1993); Fischer et al, Science 253:401-6 (1991)). Overexpression or altered activity of tyrosine phosphatases can also contribute to the symptoms and progression of various diseases (Wiener, et al., J. Natl. cancer Inst. 86:372-8 (1994); Hunter and Cooper, Ann. Rev. Biochem, 54:897-930 (1985)). Furthermore, there is increasing evidence which suggests that inhibition of these PTPases may help treat certain types of diseases such as diabetes type I and II, autoimmune disease, acute and chronic inflammation, osteoporosis and various forms of cancer.

BACKGROUND OF THE INVENTION

Protein phosphorylation is now well recognized as an important mechanism utilized by cells to transduce signals during different stages of cellular function (Fischer et al, Science 253:401-6 (1991); Flint et al., The EMBO J. 12:1937-46 (1993)). There are at least two major classes of phosphatases: (1) those that dephosphorylate proteins (or peptides) that contain a phosphate group(s) on a serine or threonine moiety (termed Ser/Thr phosphatases) and (2) those that remove a phosphate group(s) from the amino acid tyrosine (termed protein tyrosine phosphatases or PTPases).

The PTPases are a family of enzymes that can be classified into two groups: a) intracellular or nontransmembrane PTPases and b) receptor-type or transmembrane PTPases.

Intracellular PTPases: Most known intracellular type PTPases contain a single conserved catalytic phosphatase domain consisting of 220-240 amino acid residues. The regions outside the PTPase domains are believed to play important roles in localizing the intracellular PTPases subcellularly (Mauro, L.J. and Dixon, J.E. *TIBS 19*: 151-155 (1994)). The first intracellular PTPase to be purified and characterized was **PTP1B** which was isolated from human placenta (Tonks *et al., J. Biol. Chem. 263*: 6722-6730 (1988)). Shortly after, PTP1B was cloned (Charbonneau *et al., Proc. Natl. Acad. Sci. USA 86*: 5252-5256 (1989); Chernoff *et al., Proc. Natl. Acad. Sci. USA 87*: 2735-2789 (1989)). Other examples of intracellular PTPases include (1) **T-cell PTPase** (Cool *et al. Proc. Natl. Acad. Sci. USA 86*: 5257-5261 (1989)), (2) **rat brain PTPase** (Guan *et al., Proc. Natl. Acad. Sci. USA 87*:1501-1502 (1990)), (3) neuronal phosphatase **STEP** (Lombroso *et al., Proc. Natl. Acad. Sci. USA 88*: 7242-7246 (1991)), (4) ezrin-domain containing PTPases: **PTPMEG1** (Gu*et al., Proc. Natl. Acad. Sci. USA 88*: 5867-57871 (1991)), **PTPH1** (Yang and Tonks, *Proc. Natl. Acad. Sci. USA 88*: 5949-5953 (1991)), **PTPD1 and PTPD2** (Møller *et al., Proc. Natl. Acad. Sci. USA 91*: 7477-7481 (1994)), **FAP-1/BAS** (Sato *et al., Science 268*: 411-415 (1995);

Banville *et al., J. Biol. Chem. 269*: 22320-22327 (1994); Maekawa *et al., FEBS Letters 337*: 200-206 (1994)), and SH2 domain containing PTPases: **PTP1C/SH-PTP1/SHP-1** (Plutzky *et al., Proc. Natl. Acad. Sci. USA 89*: 1123-1127 (1992); Shen *et al., Nature Lond. 352*: 736-739 (1991)) and **PTP1D/Syp/SH-PTP2/SHP-2** (Vogel *et al., Science 259*: 1611-1614 (1993); Feng *et al., Science 259*: 1607-1611 (1993); Bastein *et al., Biochem. Biophys. Res. Comm. 196*: 124-133 (1993)).

Low molecular weight phosphotyrosine-protein phosphatase (**LMW-PTPase**) shows very little sequence identity to the intracellular PTPases described above. However, this enzyme belongs to the PTPase family due to the following characteristics: (i) it possesses the PTPase active site motif: Cys-Xxx-Xxx-Xxx-Xxx-Xxx-Arg (Cirri *et al., Eur. J. Biochem. 214*: 647-657 (1993)); (ii) this Cys residue forms a phospho-intermediate during the catalytic reaction similar to the situation with 'classical' PTPases (Cirri *et al., supra*; Chiarugi *et al., FEBS Lett. 310*: 9-12 (1992)); (iii) the overall folding of the molecule shows a surprising degree of similarity to that of PTP1B and *Yersinia* PTP (Su *et al., Nature 370*: 575-578 (1994)).

Receptor-type PTPases consist of a) a putative ligand-binding extracellular domain, b) a transmembrane segment, and c) an intracellular catalytic region. The structures and sizes of the putative ligand-binding extracellular domains of receptor-type PTPases are quite divergent. In contrast, the intracellular catalytic regions of receptor-type PTPases are very homologous to each other and to the intracellular PTPases. Most receptor-type PTPases have two tandemly duplicated catalytic PTPase domains.

The first receptor-type PTPases to be identified were (1) **CD45/LCA** (Ralph, S.J., *EMBO J. 6*: 1251-1257 (1987)) and (2) **LAR** (Streuli *et al., J. Exp. Med. 168*: 1523-1530 (1988)) that were recognized to belong to this class of enzymes based on homology to PTP1B (Charbonneau *et al., Proc. Natl. Acad. Sci. USA 86*: 5252-5256 (1989)). CD45 is a family of high molecular weight glycoproteins and is one

of the most abundant leukocyte cell surface glycoproteins and appears to be exclusively expressed upon cells of the hematopoietic system (Trowbridge and Thomas, *Ann. Rev. Immunol. 12*: 85-116 (1994)).

The identification of CD45 and LAR as members of the PTPase family was quickly followed by identification and cloning of several different members of the receptor-type PTPase group. Thus, 5 different PTPases, (3) **PTPα**, (4) **PTPβ**, (5) **PTPδ**, (6) **PTPε**, and (7) **PTPζ**, were identified in one early study (Krueger *et al., EMBO J. 9*: 3241-3252 (1990)). Other examples of receptor-type PTPases include (8) **PTPγ** (Barnea *et al., Mol. Cell. Biol. 13*: 1497-1506 (1995)) which, like **PTPζ** (Krueger and Saito, *Proc. Natl. Acad. Sci. USA 89*: 7417-7421 (1992)) contains a carbonic anhydrase-like domain in the extracellular region, (9) **PTPμ** (Gebbink *et al., FEBS Letters 290*: 123-130 (1991)), (10) **PTPκ** (Jiang *et al., Mol. Cell. Biol. 13*: 2942-2951 (1993)). Based on structural differences the receptor-type PTPases may be classified into subtypes (Fischer *et al., Science 253*: 401-406 (1991)): (I) CD45; (II) LAR, PTPd, (11) **PTPσ** ; (III) PTPb, (12) **SAP-1** (Matozaki *et al., J. Biol. Chem. 269*: 2075-2081 (1994)), (13) **PTP-U2/GLEPP1** (Seimiya *et al., Oncogene 10*: 1731-1738 (1995); Thomas *et al., J. Biol. Chem. 269*: 19953-19962 (1994)), and (14) **DEP-1**; (IV) PTPa,_PTPe. All receptor-type PTPases except Type IV contain two PTPase domains. Novel PTPases are continuously identified, and it is anticipated that more than 500 different species will be found in the human genome, i.e. close to the predicted size of the protein tyrosine kinase superfamily (Hanks and Hunter, *FASEB J. 9*: 576-596 (1995)).

PTPases are the biological counterparts to protein tyrosine kinases (PTKs). Therefore, one important function of PTPases is to control, down-regulate, the activity of PTKs. However, a more complex picture of the function of PTPases now emerges. Several studies have shown that some PTPases may actually act as positive mediators of cellular signalling. As an example, the SH2 domain-containing PTP1D seems to act as a positive mediator in insulin-stimulated Ras activation (Noguchi *et al., Mol. Cell. Biol. 14*: 6674-6682 (1994)) and of growth

factor-induced mitogenic signal transduction (Xiao *et al., J. Biol. Chem. 269*: 21244-21248 (1994)), whereas the homologous PTP1C seems to act as a negative regulator of growth factor-stimulated proliferation (Bignon and Siminovitch, *Clin.Immunol. Immunopathol. 73*: 168-179 (1994)). Another example of PTPases as positive regulators has been provided by studies designed to define the activation of the Src-family of tyrosine kinases. In particular, several lines of evidence indicate that CD45 is positively regulating the activation of hematopoietic cells, possibly through dephosphorylation of the C-terminal tyrosine of Fyn and Lck (Chan *et al., Annu. Rev. Immunol. 12*: 555-592 (1994)).

Dual specificity protein tyrosine phosphatases (dsPTPases) define a subclass within the PTPases family that can hydrolyze phosphate from phosphortyrosine as well as from phosphor-serine/threonine. dsPTPases contain the signature sequence of PTPases: His-Cys-Xxx-Xxx-Gly-Xxx-Xxx-Arg. At least three dsPTPases have been shown to dephosphorylate and inactivate extracellular signal-regulated kinase (ERKs)/mitogen-activated protein kinase (MAPK): **MAPK phosphatase** (CL100, 3CH134) (Charles *et al., Proc. Natl. Acad. Sci. USA 90*: 5292-5296 (1993)); **PAC-1** (Ward *et al., Nature 367*: 651-654 (1994)); **rVH6** (Mourey *et al., J. Biol. Chem. 271*: 3795-3802 (1996)). Transcription of dsPTPases are induced by different stimuli, e.g. oxidative stress or heat shock (Ishibashi *et al., J. Biol. Chem. 269*: 29897-29902 (1994); Keyse and Emslie, *Nature 359*: 644-647 (1992)). Further, they may be involved in regulation of the cell cycle: **cdc25** (Millar and Russell, *Cell 68*: 407-410 (1992)); **KAP** (Hannon *et al., Proc. Natl. Acad. Sci. USA 91*: 1731-1735 (1994)). Interestingly, tyrosine dephosphorylation of cdc2 by a dual specific phosphatase, cdc25, is required for induction of mitosis in yeast (review by Walton and Dixon, *Annu. Rev. Biochem. 62*: 101-120 (1993)).

PTPases were originally identified and purified from cell and tissue lysates using a variety of artificial substrates and therefore their natural function of dephosphorylation was not well known. Since tyrosine phosphorylation by tyrosine kinases is usually

associated with cell proliferation, cell transformation and cell differentiation, it was assumed that PTPases were also associated with these events.

This association has now been proven to be the case with many PTPases. PTP1B, a phosphatase whose structure was recently elucidated (Barford et al., Science 263:1397-1404 (1994)) has been shown to be involved in insulin-induced oocyte maturation (Flint et al., The EMBO J. 12:1937-46 (1993)) and recently it has been suggested that the overexpression of this enzyme may be involved in $p185^{c\text{-}erb\ B2}$-associated breast and ovarian cancers (Wiener, et al., J. Natl. cancer Inst. 86:372-8 (1994); Weiner et al., Am. J. Obstet. Gynecol. 170:1177-883 (1994)). The insulin-induced oocyte maturation mechanism has been correlated with the ability of PTP1B to block activation of S6 kinase. The association with cancer is recent evidence which suggests that overexpression of PTP1B is statistically correlated with increased levels of $p185^{c\text{-}erb\ B2}$ in ovarian and breast cancer. The role of PTP1B in the etiology and progression of the disease has not yet been elucidated. Inhibitors of PTP1B may therefore help clarify the role of PTP1B in cancer and in some cases provide therapeutic treatment for certain forms of cancer.

The activity of a number of other newly discussed phosphatases are currently under investigation. Two of these: SHP-1 and Syp/PTP1D/SHPTP2/PTP2C/SHP-2 have recently been implicated in the activation of Platelet Derived Growth Factor and Epidermal Growth Factor induced responses (Li et al., Mole. Cell. Biol. 14:509-17 (1994)). Since both growth factors are involved in normal cell processing as well as disease states such as cancer and arteriosclerosis, it is hypothesized that inhibitors of these phosphatases would also show therapeutic efficacy. Accordingly, the compounds of the present invention which exhibit inhibitory activity against various PTPases, are indicated in the treatment or management of the foregoing diseases.

PTPases: the insulin receptor signalling pathway/diabetes

Insulin is an important regulator of different metabolic processes and plays a key role in the control of blood glucose. Defects related to its synthesis or signalling

lead to diabetes mellitus. Binding of insulin to its receptor causes rapid (auto)phosphorylation of several tyrosine residues in the intracellular part of the b-subunit. Three closely positioned tyrosine residues (the tyrosine-1150 domain) must all be phosphorylated to obtain full activity of the insulin receptor tyrosine kinase (IRTK) which transmits the signal further downstream by tyrosine phosphorylation of other cellular substrates, including insulin receptor substrate-1 (IRS-1) (Wilden *et al., J. Biol. Chem. 267*: 16660-16668 (1992); Myers and White, *Diabetes 42*: 643-650 (1993); Lee and Pilch, *Am. J. Physiol. 266*: C319-C334 (1994); White *et al., J. Biol. Chem. 263*: 2969-2980 (1988)). The structural basis for the function of the tyrosine-triplet has been provided by recent X-ray crystallographic studies of IRTK that showed tyrosine-1150 to be autoinhibitory in its unphosphorylated state (Hubbard *et al., Nature 372*: 746-754 (1994)).

Several studies clearly indicate that the activity of the auto-phosphorylated IRTK can be reversed by dephosphorylation *in vitro* (reviewed in Goldstein, *Receptor 3*: 1-15 (1993); Mooney and Anderson, *J. Biol. Chem. 264*: 6850-6857 (1989)), with the tri-phosphorylated tyrosine-1150 domain being the most sensitive target for protein-tyrosine phosphatases (PTPases) as compared to the di- and mono-phosphorylated forms (King *et al., Biochem. J. 275*: 413-418 (1991)). It is, therefore, tempting to speculate that this tyrosine-triplet functions as a control switch of IRTK activity. Indeed, the IRTK appears to be tightly regulated by PTP-mediated dephosphorylation *in vivo* (Khan *et al., J. Biol. Chem. 264*: 12931-12940 (1989); Faure *et al., J. Biol. Chem. 267*: 11215-11221 (1992); Rothenberg *et al., J. Biol. Chem. 266*: 8302-8311 (1991)). The intimate coupling of PTPases to the insulin signalling pathway is further evidenced by the finding that insulin differentially regulates PTPase activity in rat hepatoma cells (Meyerovitch *et al., Biochemistry 31*: 10338-10344 (1992)) and in livers from alloxan diabetic rats (Boylan *et al., J. Clin. Invest. 90*: 174-179 (1992)).

Relatively little is known about the identity of the PTPases involved in IRTK regulation. However, the existence of PTPases with activity towards the insulin

receptor can be demonstrated as indicated above. Further, when the strong PTPase-inhibitor pervanadate is added to whole cells an almost full insulin response can be obtained in adipocytes (Fantus *et al.*, *Biochemistry 28*: 8864-8871 (1989); Eriksson *et al.*, *Diabetologia 39*: 235-242 (1995)) and skeletal muscle (Leighton *et al.*, *Biochem. J. 276*: 289-292 (1991)). In addition, recent studies show that a new class of peroxovanadium compounds act as potent hypoglycemic compounds *in vivo* (Posner *et al.*,*supra*). Two of these compounds were demonstrated to be more potent inhibitors of dephosphorylation of the insulin receptor than of the EGF-receptor.

It was recently found that the ubiquitously expressed SH2 domain containing PTPase, PTP1D (Vogel *et al.*, 1993, *supra*), associates with and dephosphorylates IRS-1, but apparently not the IR itself (Kuhné *et al.*, *J. Biol. Chem. 268*: 11479-11481 (1993); (Kuhné *et al.*, *J. Biol. Chem. 269*: 15833-15837 (1994)).

Previous studies suggest that the PTPases responsible for IRTK regulation belong to the class of membrane-associated (Faure *et al.*, *J. Biol. Chem. 267*: 11215-11221 (1992)) and glycosylated molecules (Häring *et al.*, *Biochemistry 23*: 3298-3306 (1984); Sale, *Adv. Prot. Phosphatases 6*: 159-186 (1991)). Hashimoto *et al.* have proposed that LAR might play a role in the physiological regulation of insulin receptors in intact cells (Hashimoto *et al.*, *J. Biol. Chem. 267*: 13811-13814 (1992)). Their conclusion was reached by comparing the rate of dephosphoryl-ation/inactivation of purified IR using recombinant PTP1B as well as the cytoplasmic domains of LAR and PTPa. Antisense inhibition was recently used to study the effect of LAR on insulin signalling in a rat hepatoma cell line (Kulas *et al.*, *J. Biol. Chem. 270*: 2435-2438 (1995)). A suppression of LAR protein levels by about 60 percent was paralleled by an approximately 150 percent increase in insulin-induced auto-phosphorylation. However, only a modest 35 percent increase in IRTK activity was observed, whereas the insulin-dependent phosphatidylinositol 3-kinase (PI 3-kinase) activity was significantly increased by 350 percent. Reduced LAR levels did not alter the basal level of IRTK tyrosine

phosphorylation or activity. The authors speculate that LAR could specifically dephosphorylate tyrosine residues that are critical for PI 3-kinase activation either on the insulin receptor itself or on a downstream substrate.

While previous reports indicate a role of PTPa in signal transduction through src activation (Zheng *et al., Nature 359*: 336-339 (1992); den Hertog *et al., EMBO J. 12*: 3789-3798 (1993)) and interaction with GRB-2 (den Hertog *et al., EMBO J. 13*: 3020-3032 (1994); Su *et al., J. Biol. Chem. 269*: 18731-18734 (1994)), a recent study suggests a function for this phosphatase and its close relative PTPe as negative regulators of the insulin receptor signal (Møller *et al.*, 1995 *supra*). This study also indicates that receptor-like PTPases play a significant role in regulating the IRTK, whereas intracellular PTPases seem to have little, if any, activity towards the insulin receptor. While it appears that the target of the negative regulatory activity of PTPases a and e is the receptor itself, the downmodulating effect of the intracellular TC-PTP seems to be due to a downstream function in the IR-activated signal. Although PTP1B and TC-PTP are closely related, PTP1B had only little influence on the phosphorylation pattern of insulin-treated cells. Both PTPases have distinct structural features that determine their subcellular localization and thereby their access to defined cellular substrates (Frangione *et al., Cell 68*: 545-560 (1992); Faure and Posner, *Glia 9*: 311-314 (1993)). Therefore, the lack of activity of PTP1B and TC-PTP towards the IRTK may, at least in part, be explained by the fact that they do not co-localize with the activated insulin receptor. In support of this view, PTP1B and TC-PTP have been excluded as candidates for the IR-associated PTPases in hepatocytes based on subcellular localization studies (Faure *et al., J. Biol. Chem. 267*: 11215-11221 (1992)).

The transmembrane PTPase CD45, which is believed to be hematopoietic cell-specific, was in a recent study found to negatively regulate the insulin receptor tyrosine kinase in the human multiple myeloma cell line U266 (Kulas *et al., J. Biol. Chem. 271*: 755-760 (1996)).

PTPases: somatostatin

Somatostatin inhibits several biological functions including cellular proliferation (Lamberts *et al., Molec. Endocrinol. 8*: 1289-1297 (1994)). While part of the antiproliferative activities of somatostatin are secondary to its inhibition of hormone and growth factor secretion (e.g. growth hormone and epidermal growth factor), other antiproliferative effects of somatostatin are due to a direct effect on the target cells. As an example, somatostatin analogs inhibit the growth of pancreatic cancer presumably via stimulation of a single PTPase, or a subset of PTPases, rather than a general activation of PTPase levels in the cells (Liebow *et al., Proc. Natl. Acad. Sci. USA 86*: 2003-2007 (1989); Colas *et al., Eur. J. Biochem. 207*: 1017-1024 (1992)). In a recent study it was found that somatostatin stimulation of somatostatin receptors SSTR1, but not SSTR2, stably expressed in CHO-K1 cells can stimulate PTPase activity and that this stimulation is pertussis toxin-sensitive. Whether the inhibitory effect of somatostatin on hormone and growth factor secretion is caused by a similar stimulation of PTPase activity in hormone producing cells remains to be determined.

PTPases: the immune system/autoimmunity

Several studies suggest that the receptor-type PTPase CD45 plays a critical role not only for initiation of T cell activation, but also for maintaining the T cell receptor-mediated signalling cascade. These studies are reviewed in: (Weiss A., *Ann. Rev. Genet. 25*: 487-510 (1991); Chan *et al., Annu. Rev. Immunol. 12*: 555-592 (1994); Trowbridge and Thomas, *Annu. Rev. Immunol. 12*: 85-116 (1994)).
CD45 is one of the most abundant of the cell surface glycoproteins and is expressed exclusively on hemopoetic cells. In T cells, it has been shown that CD45 is one of the critical components of the signal transduction machinery of lymphocytes. In particular, evidence has suggested that CD45 phosphatase plays a pivotal role in antigen-stimulated proliferation of T lymphocytes after an antigen has bound to the T cell receptor (Trowbridge, *Ann. Rev. Immunol*, 12:85-116 (1994)). Several studies suggest

that the PTPase activity of CD45 plays a role in the activation of Lck, a lymphocyte-specific member of the Src family protein-tyrosine kinase (Mustelin etal., Proc. Natl. Acad. Sci. USA 86: 6302-6306 (1989); Ostergaard et al., Proc. Natl. Acad. Sci. USA 86: 8959-8963 (1989)). These authors hypothesized that the phosphatase activity of CD45 activates Lck by dephosphorylation of a C-terminal tyrosine residue, which may, in turn, be related to T-cell activation. In a recent study it was found that recombinant p56lck specifically associates with recombinant CD45 cytoplasmic domain protein, but not to the cytoplasmic domain of the related PTPa (Ng et al., *J. Biol. Chem.* 271: 1295-1300 (1996)). The p56lck-CD45 interaction seems to be mediated via a nonconventional SH2 domain interaction not requiring phosphotyrosine. In immature B cells, another member of the Src family protein-tyrosine kinases, Fyn, seems to be a selective substrate for CD45 compared to Lck and Syk (Katagiri et al., *J. Biol. Chem.* 270: 27987-27990 (1995)).

Studies using transgenic mice with a mutation for the CD45-exon6 exhibited lacked mature T cells. These mice did not respond to an antigenic challenge with the typical T cell mediated response (Kishihara *et* al., *Cell* 74:143-56 (1993)). Inhibitors of CD45 phosphatase would therefore be very effective therapeutic agents in conditions that are associated with autoimmune disease.

CD45 has also been shown to be essential for the antibody mediated degranulation of mast cells (Berger *et* al., *J. Exp. Med.* 180:471-6 (1994)). These studies were also done with mice that were CD45-deficient. In this case, an IgE-mediated degranulation was demonstrated in wild type but not CD45-deficient T cells from mice. These data suggest that CD45 inhibitors could also play a role in the symptomatic or therapeutic treatment of allergic disorders.

Another recently discovered PTPase, an inducible lymphoid-specific protein tyrosine phosphatase (HePTP) has also been implicated in the immune response. This phosphatase is expressed in both resting T and B lymphocytes, but not non-hemopoetic cells. Upon stimulation of these cells, mRNA levels from the HePTP gene increase

10-15 fold (Zanke *et al.*, *Eur. J. Immunol.* 22:235-239 (1992)). In both T and B cells HePTP may function during sustained stimulation to modulate the immune response through dephosphorylation of specific residues. Its exact role, however remains to be defined.

Likewise, the hematopoietic cell specific PTP1C seems to act as a negative regulator and play an essential role in immune cell development.In accordance with the above-mentioned important function of CD45, HePTP and PTP1C, selective PTPase inhibitors may be attractive drug candidates both as immunosuppressors and as immunostimulants. One recent study illustrates the potential of PTPase inhibitors as immunmodulators by demonstrating the capacity of the vanadium-based PTPase inhibitor, BMLOV, to induce apparent B cell selective apoptosis compared to T cells (Schieven et al., *J. Biol. Chem.* 270: 20824-20831 (1995)).

PTPases: cell-cell interactions/cancer

Focal adhesion plaques, an *in vitro* phenomenon in which specific contact points are formed when fibroblasts grow on appropriate substrates, seem to mimic, at least in part, cells and their natural surroundings. Several focal adhesion proteins are phosphorylated on tyrosine residues when fibroblasts adhere to and spread on extracellular matrix (Gumbiner, *Neuron 11*, 551-564 (1993)). However, aberrant tyrosine phosphorylation of these proteins can lead to cellular transformation. The intimate association between PTPases and focal adhesions is supported by the finding of several intracellular PTPases with ezrin-like N-terminal domains, e.g. PTPMEG1 (Gu *et al.*, *Proc. Natl. Acad. Sci. USA 88*: 5867-5871 (1991)), PTPH1 (Yang and Tonks, *Proc. Natl. Acad. Sci. USA 88*: 5949-5953 (1991)) and PTPD1 (Møller *et al., Proc. Natl. Acad. Sci. USA 91*: 7477-7481 (1994)). The ezrin-like domain show similarity to several proteins that are believed to act as links between the cell membrane and the cytoskeleton. PTPD1 was found to be phosphorylated

by and associated with c-src *in vitro* and is hypothesized to be involved in the regulation of phosphorylation of focal adhesions (Møller *et al.*, *supra*).

PTPases may oppose the action of tyrosine kinases, including those responsible for phosphorylation of focal adhesion proteins, and may therefore function as natural inhibitors of transformation. TC-PTP, and especially the truncated form of this enzyme (Cool *et al.*, *Proc. Natl. Acad. Sci. USA 87:* 7280-7284 (1990)), can inhibit the transforming activity of v-*erb* and v-*fms* (Lammers *et al.*, *J. Biol. Chem. 268:* 22456-22462 (1993); Zander *et al.*, *Oncogene 8:* 1175-1182 (1993)). Moreover, it was found that transformation by the oncogenic form of the *HER2/neu* gene was suppressed in NIH 3T3 fribroblasts overexpressing PTP1B (Brown-Shimer *et al.*, *Cancer Res. 52:* 478-482 (1992)).

The expression level of PTP1B was found to be increased in a mammary cell line transformed with *neu* (Zhay *et al.*, *Cancer Res. 53:* 2272-2278 (1993)). The intimate relationship between tyrosine kinases and PTPases in the development of cancer is further evidenced by the recent finding that PTPe is highly expressed in murine mammary tumors in transgenic mice over-expressing c-*neu* and v-Ha-*ras*, but not c-*myc* or *int-2* (Elson and Leder, *J. Biol. Chem. 270:* 26116-26122 (1995)). Further, the human gene encoding PTPg was mapped to 3p21, a chromosomal region which is frequently deleted in renal and lung carcinomas (LaForgia *et al.*, *Proc. Natl. Acad. Sci. USA 88*: 5036-5040 (1991)).

In this context, it seems significant that PTPases appear to be involved in controlling the growth of fibroblasts. In a recent study it was found that Swiss 3T3 cells harvested at high density contain a membrane-associated PTPase whose activity on an average is 8-fold higher than that of cells harvested at low or medium density (Pallen and Tong, *Proc. Natl. Acad. Sci. USA 88*: 6996-7000 (1991)). It was hypothesized by the authors that density-dependent inhibition of cell growth involves the regulated elevation of the activity of the PTPase(s) in question. In accordance with this view, a novel membrane-bound, receptor-type

PTPase, DEP-1, showed enhanced (>=10-fold) expression levels with increasing cell density of WI-38 human embryonic lung fibroblasts and in the AG1518 fibroblast cell line (Östman *et al., Proc. Natl. Acad. Sci. USA 91*: 9680-9684 (1994)).

Two closely related receptor-type PTPases, PTPκ and PTPμ, can mediate homophilic cell-cell interaction when expressed in non-adherent insect cells, suggesting that these PTPases might have a normal physiological function in cell-to-cell signalling (Gebbink *et al., J. Biol. Chem. 268*: 16101-16104 (1993); Brady-Kalnay *et al., J. Cell Biol. 122*: 961-972 (1993); Sap *et al., Mol. Cell. Biol. 14*: 1-9 (1994)). Interestingly, PTPk and PTPμ do not interact with each other, despite their structural similarity (Zondag *et al., J. Biol. Chem. 270*: 14247-14250 (1995)). From the studies described above it is apparent that PTPases may play an important role in regulating normal cell growth. However, as pointed out above, recent studies indicate that PTPases may also function as positive mediators of intracellular signalling and thereby induce or enhance mitogenic responses. Increased activity of certain PTPases might therefore result in cellular transformation and tumor formation. Indeed, in one study over-expression of PTPα was found to lead to transformation of rat embryo fibroblasts (Zheng, *supra*). In addition, a novel PTP, SAP-1, was found to be highly expressed in pancreatic and colorectal cancer cells. SAP-1 is mapped to chromosome 19 region q13.4 and might be related to carcinoembryonic antigen mapped to 19q13.2 (Uchida *et al., J. Biol. Chem. 269*: 12220-12228 (1994)). Further, the dsPTPase, cdc25, dephosphorylates cdc2 at Thr14/Tyr-15 and thereby functions as positive regulator of mitosis (reviewed by Hunter, *Cell 80*: 225-236 (1995)). Inhibitors of specific PTPases are therefore likely to be of significant therapeutic value in the treatment of certain forms of cancer.

<u>PTPases: platelet aggregation</u>

Recent studies indicate that PTPases are centrally involved in platelet aggregation. Agonist-induced platelet activation results in calpain-catalyzed cleavage of PTP1B with a concomitant 2-fold stimulation of PTPase activity (Frangioni *et al., EMBO J. 12:* 4843-4856 (1993)). The cleavage of PTP1B leads to subcellular relocation of the enzyme and correlates with the transition from reversible to irreversible platelet aggregation in platelet-rich plasma. In addition, the SH2 domain containing PTPase, SHP-1, was found to translocate to the cytoskeleton in platelets after thrombin stimulation in an aggregation-dependent manner (Li *et al., FEBS Lett. 343:* 89-93 (1994)).

Although some details in the above two studies were recently questioned there is over-all agreement that PTP1B and SHP-1 play significant functional roles in platelet aggregation (Ezumi *et al., J. Biol. Chem. 270:* 11927-11934 (1995)). In accordance with these observations, treatment of platelets with the PTPase inhibitor pervanadate leads to significant increase in tyrosine phosphorylation, secretion and aggregation (Pumiglia *et al., Biochem. J. 286:* 441-449 (1992)).

PTPases: osteoporosis

The rate of bone formation is determined by the number and the activity of osteoblasts, which in term are determined by the rate of proliferation and differentiation of osteoblast progenitor cells, respectively. Histomorphometric studies indicate that the osteoblast number is the primary determinant of the rate of bone formation in humans (Gruber *et al., Mineral Electrolyte Metab. 12*: 246-254 (1987); reviewed in Lau *et al., Biochem. J. 257*: 23-36 (1989)). Acid phosphatases/PTPases may be involved in negative regulation of osteoblast proliferation. Thus, fluoride, which has phosphatase inhibitory activity, has been found to increase spinal bone density in osteoporotics by increasing osteoblast proliferation (Lau *et al., supra*). Consistent with this observation, an osteoblastic acid phosphatase with PTPase activity was found to be highly sensitive to mitogenic concentrations of fluoride (Lau *et al., J. Biol. Chem. 260*: 4653-4660

(1985); Lau *et al., J. Biol. Chem. 262*: 1389-1397 (1987); Lau *et al., Adv. Protein Phosphatases 4*: 165-198 (1987)). Interestingly, it was recently found that the level of membrane-bound PTPase activity was increased dramatically when the osteoblast-like cell line UMR 106.06 was grown on collagen type-I matrix compared to uncoated tissue culture plates. Since a significant increase in PTPase activity was observed in density-dependent growth arrested fibroblasts (Pallen and Tong, *Proc. Natl. Acad. Sci. 88*: 6996-7000 (1991)), it might be speculated that the increased PTPase activity directly inhibits cell growth. The mitogenic action of fluoride and other phosphatase inhibitors (molybdate and vanadate) may thus be explained by their inhibition of acid phosphatases/PTPases that negatively regulate the cell proliferation of osteoblasts. The complex nature of the involvement of PTPases in bone formation is further suggested by the recent identification of a novel parathyroid regulated, receptor-like PTPase, OST-PTP, expressed in bone and testis (Mauro *et al., J. Biol. Chem. 269*: 30659-30667 (1994)). OST-PTP is up-regulated following differentiation and matrix formation of primary osteoblasts and subsequently down-regulated in the osteoblasts which are actively mineralizing bone in culture. It may be hypothesized that PTPase inhibitors may prevent differentiation via inhibition of OST-PTP or other PTPases thereby leading to continued proliferation. This would be in agreement with the above-mentioned effects of fluoride and the observation that the tyrosine phosphatase inhibitor orthovanadate appears to enhance osteoblast proliferation and matrix formation (Lau *et al., Endocrinology 116*: 2463-2468 (1988)). In addition, it was recently observed that vanadate, vanadyl and pervanadate all increased the growth of the osteoblast-like cell line UMR106. Vanadyl and pervanadate were stronger stimulators of cell growth than vanadate. Only vanadate was able to regulate the cell differentiation as measured by cell alkaline phosphatase activity (Cortizo *et al., Mol. Cell. Biochem. 145*: 97-102 (1995)).

PTPases; microorganisms

Dixon and coworkers have called attention to the fact that PTPases may be a key element in the pathogenic properties of *Yersinia* (reviewed in Clemens *et al. Molecular Microbiology 5*: 2617-2620 (1991)). This finding was rather surprising since tyrosine phosphate is thought to be absent in bacteria. The genus *Yersinia* comprises 3 species: *Y. pestis* (responsible for the bubonic plague), *Y. pseudoturberculosis* and *Y. enterocolitica* (causing enteritis and mesenteric lymphadenitis). Interestingly, a dual-specificity phosphatase, VH1, has been identified in Vaccinia virus (Guan *et al., Nature 350*: 359-263 (1991)). These observations indicate that PTPases may play critical roles in microbial and parasitic infections, and they further point to PTPase inhibitors as a novel, putative treatment principle of infectious diseases.

SUMMARY OF THE INVENTION

The present invention relates to compounds of the general formula I, wherein A, R_1, R_2, R_3, R_4, R_{16} and R_{17} are as defined in the detailed part of the present description, wherein such compounds are pharmacologically useful inhibitors of Protein Tyrosine Phosphatases (PTPases) such as PTP1B, CD45, SHP-1, SHP-2, PTPα, LAR and HePTP or the like.

The present compounds are useful for the treatment, prevention, elimination, alleviation or amelioration of an indication related to type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance, obesity, immune dysfunctions including autoimmunity and AIDS, diseases with dysfunctions of the coagulation system, allergic diseases including asthma, osteoporosis, proliferative disorders including cancer and psoriasis, diseases with decreased or increased synthesis or effects of growth hormone, diseases with decreased or increased synthesis of hormones or cytokines that regulate the release of/or response to growth hormone, diseases of the brain including Alzheimer's disease and schizophrenia, and infectious diseases.

In another aspect, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of the

general formula I or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

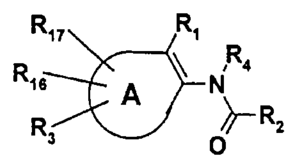
In another aspect of the present invention there is provided a method of treating type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance, obesity, immune dysfunctions including autoimmunity and AIDS, diseases with dysfunctions of the coagulation system, allergic diseases including asthma, osteoporosis, proliferative disorders including cancer and psoriasis, diseases with decreased or increased synthesis or effects of growth hormone, diseases with decreased or increased synthesis of hormones or cytokines that regulate the release of/or response to growth hormone, diseases of the brain including Alzheimer's disease and schizophrenia, and infectious diseases.

The method of treatment may be described as the treatment, prevention, elimination, alleviation or amelioration of one of the above indications, which comprises the step of administering to the said subject a neurologically effective amount of a compound of the invention, or a pharmaceutically acceptable salt thereof.

A further aspect of the invention relates to the use of a compound of the present invention for the preparation of a pharmaceutical composition for the treatment of all type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance, obesity, immune dysfunctions including autoimmunity and AIDS, diseases with dysfunctions of the coagulation system, allergic diseases including asthma, osteoporosis, proliferative disorders including cancer and psoriasis, diseases with decreased or increased synthesis or effects of growth hormone, diseases with decreased or increased synthesis of hormones or cytokines that regulate the release of/or response to growth hormone, diseases of the brain including Alzheimer's disease and schizophrenia, and infectious diseases.

DESCRIPTION OF THE INVENTION

The present invention relates to Compounds of the Formula 1 wherein A, R_1, R_2, R_3, R_4, R_{16} and R_{17} are defined below;

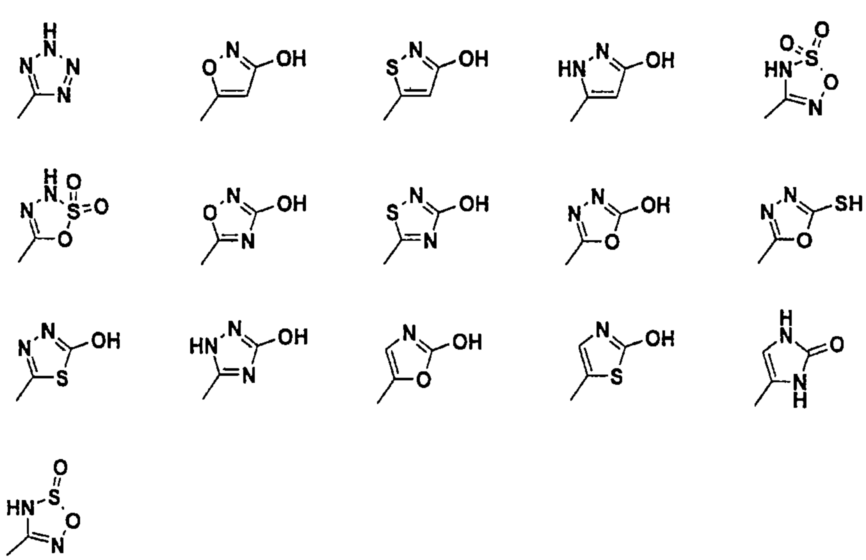


Formula 1

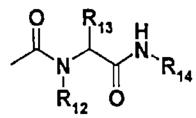
In the above Formula 1

A is together with the double bond in Formula 1 furanyl, thiophenyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, furazanyl or 1,2,3-triazolyl;

R_1 is hydrogen, COR_5, OR_6, CF_3, nitro, cyano, SO_3H, $SO_2NR_7R_8$, $PO(OH)_2$, $CH_2PO(OH)_2$, $CHFPO(OH)_2$, $CF_2PO(OH)_2$, $C(=NH)NH_2$, NR_7R_8 or selected from the following 5-membered heterocycles:

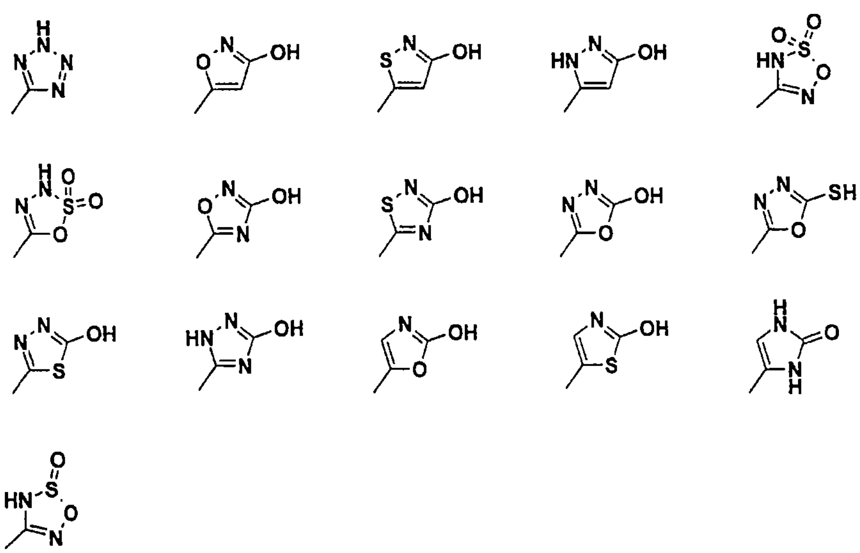


or R_1 is



wherein R_{12}, R_{13}, and R_{14} are independently hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl and the alkyl and aryl groups are optionally substituted;

R_2 is COR_5, OR_6, CF_3, nitro, cyano, SO_3H, $SO_2NR_7R_8$, $PO(OH)_2$, $CH_2PO(OH)_2$, $CHFPO(OH)_2$, $CF_2PO(OH)_2$, $C(=NH)NH_2$, NR_7R_8 , or selected from the following 5-membered heterocycles:



R_3, R_{16} and R_{17} are independently hydrogen, halo, nitro, cyano, trihalomethyl, C_1-C_6alkyl, aryl, arylC_1-C_6-alkyl, hydroxy, oxo, carboxy, carboxyC_1-C_6alkyl, C_1-C_6alkyloxycarbonyl, aryloxycarbonyl, arylC_1-C_6alkyloxycarbonyl, C_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, aryloxy, arylC_1-C_6alkyloxy, arylC_1-C_6alkyloxyC_1-C_6alkyl, thio, C_1-C_6alkylthio, C_1-C_6alkylthioC_1-C_6alkyl, arylthio, arylC_1-C_6alkylthio, arylC_1-C_6alkylthioC_1-C_6alkyl, NR_7R_8, C_1-C_6alkylaminoC_1-C_6alkyl, arylC_1-C_6alkylaminoC_1-C_6alkyl, di(arylC_1-

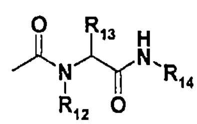
C_6alkyl)aminoC_1-C_6alkyl, C_1-C_6alkylcarbonyl, C_1-C_6alkylcarbonyl-C_1-C_6alkyl, arylC_1-C_6alkylcarbonyl, arylC_1-C_6alkylcarbonylC_1-C_6alkyl, C_1-C_6alkylcarboxy, C_1-C_6alkylcarboxyC_1-C_6-alkyl, arylcarboxy, arylcarboxyC_1-C_6-alkyl, arylC_1-C_6alkyl-carboxy, arylC_1-C_6alkylcarboxyC_1-C_6alkyl, C_1-C_6alkylcarbonylamino, C_1-C_6alkylcarbonylaminoC_1-C_6alkyl, -carbonylNR_7C_1-C_6alkylCOR_{11}, arylC_1-C_6alkylcarbonylamino, arylC_1-C_6alkylcarbonylaminoC_1-C_6alkyl, $CONR_7R_8$, or C_1-C_6alkyl$CONR_7R_8$ wherein the alkyl and aryl groups are optionally substituted and R_{11} is NR_7R_8, or C_1-C_6alkylNR_7R_8; or, when R_{16} and R_{17} are hydrogen, R_3 is A-B-C-D-C_1-C_6alkyl, wherein

A is C_1-C_8alkyl, aryl or arylC_1-C_6alkyl;

B is amino, thio, SO, SO_2 or oxo;

C is C_1-C_8alkyl, amino;

D is a chemical bond, amino or C_1-C_8alkyl wherein the alkyl and aryl groups are optionally substituted; or



wherein R_{12}, R_{13}, and R_{14} are independently hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl and the alkyl and aryl groups are optionally substituted;

R_4 is hydrogen, hydroxy, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, NR_7R_8, C_1-C_6alkyloxy; wherein the alkyl and aryl groups are optionally substituted;

R_5 is hydroxy, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkyloxy, C_1-C_6alkyl-oxyC_1-C_6alkyloxy, aryloxy, arylC_1-C_6alkyloxy, CF_3, NR_7R_8; wherein the alkyl and aryl groups are optionally substituted;

R_6 is hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl; wherein the alkyl and aryl groups are optionally substituted;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6alkyl, adamantyl, aryl, arylC$_1$-C_6alkyl, C_1-C_6alkylcarbonyl, arylcarbonyl, arylC$_1$-C_6alkylcarbonyl, C_1-C_6alkylcarboxy or arylC$_1$-C_6alkylcarboxy wherein the alkyl and aryl groups are optionally substituted; or

R_7 and R_8 are taken together with the nitrogen to which they are attached forming a saturated, partially saturated or aromatic cyclic, bicyclic or tricyclic ring system containing 3 to 14 carbon atoms and from 0 to 3 additional heteroatoms selected from nitrogen, oxygen or sulfur, the ring system can optionally be substituted with at least one C_1-C_6alkyl, aryl, arylC$_1$-C_6alkyl, hydroxy, oxo, C_1-C_6alkyloxy, arylC$_1$-C_6alkyloxy, C_1-C_6alkyloxyC$_1$-C_6alkyl, NR_9R_{10} or C_1-C_6alkylaminoC$_1$-C_6alkyl, wherein R_9 and R_{10} are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC$_1$-C_6alkyl, C_1-C_6alkylcarbonyl, arylcarbonyl, arylC$_1$-C_6alkylcarbonyl, C_1-C_6alkylcarboxy or arylC$_1$-C_6alkylcarboxy; wherein the alkyl and aryl groups are optionally substituted; or

R_7 and R_8 are independently a saturated or partial saturated cyclic 5, 6 or 7 membered amine, imide or lactam;

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

DEFINITIONS

Signal transduction is a collective term used to define all cellular processes that follow the activation of a given cell or tissue. Examples of signal transduction, which are not intended to be in any way limiting to the scope of the invention claimed, are cellular events that are induced by polypeptide hormones and growth factors (e.g. insulin, insulin-like growth factors I and II, growth hormone, epidermal growth factor, platelet-derived growth factor), cytokines (e.g. interleukins), extracellular matrix components, and cell-cell interactions.

Phosphotyrosine recognition units/tyrosine phosphate recognition units/pTyr recognition units are defined as areas or domains of proteins or glycoproteins that have affinity for molecules containing phosphorylated tyrosine residues (pTyr). Examples of pTyr recognition units, which are not intended to be in any way limiting to the scope of the invention claimed, are: PTPases, SH2 domains and PTB domains.

PTPases are defined as enzymes with the capacity to dephosphorylate pTyr-containing proteins or glycoproteins. Examples of PTPases, which are not intended to be in any way limiting to the scope of the invention claimed, are: 'classical'. PTPases (intracellular PTPases (e.g. PTP1B, TC-PTP, PTP1C, PTP1D, PTPD1, PTPD2) and receptor-type PTPases (e.g. PTPα, PTPε, PTPβ, PTPγ, CD45, PTPκ, PTPμ), dual specificty phosphatases (VH1, VHR, cdc25), LMW-PTPases or acid phosphatases.

SH2 domains (Src homology 2 domains) are non-catalytic protein modules that bind to pTyr (phosphotyrosine residue) containing proteins, i.e. SH2 domains are pTyr recognition units. SH2 domains, which consist of ~100 amino acid residues, are found in a number of different molecules involved in signal transduction processes. The following is a non-limiting list of proteins containing SH2 domains: Src, Hck, Lck, Syk, Zap70, SHP-1, SHP-2, STATs, Grb-2, Shc, p85/PI3K, Gap, vav (see Russell et al, FEBS Lett. 304:15-20 (1992); Pawson, Nature 373: 573-580 (1995); Sawyer, Biopolymers (Peptide Science) 47: 243-261 (1998); and references herein).

As used herein, the term "attached" or "-" (e.g. $-COR_{11}$ which indicates the carbonyl attachment point to the scaffold) signifies a stable covalent bond, certain preferred points of attachment points being apparent to those skilled in the art.

The terms "halogen" or "halo" include fluorine, chlorine, bromine, and iodine.

The term "alkyl" includes C_1-C_6 or C_1-C_8 straight chain saturated and C_2-C_8 unsaturated aliphatic hydrocarbon groups, C_1-C_6 or C_1-C_8 branched saturated and C_2-C_6 or C_2-C_8 unsaturated aliphatic hydrocarbon groups, C_3-C_6 or C_3-C_8 cyclic saturated and C_5-C_6 or C_5-C_8 unsaturated aliphatic hydrocarbon groups, and C_1-C_6 or C_1-C_8 straight

chain or branched saturated and C_2-C_6 or C_2-C_8 straight chain or branched unsaturated aliphatic hydrocarbon groups substituted with C_3-C_6 cyclic saturated and unsaturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, this definition shall include but is not limited to methyl (Me), ethyl (Et), propyl (Pr), butyl (Bu), pentyl, hexyl, heptyl, octyl, ethenyl, propenyl, butenyl, penentyl, hexenyl, octenyl, isopropyl (i-Pr), isobutyl (i-Bu), *tert*-butyl (*t*-Bu), *sec*-butyl (*s*-Bu), isopentyl, neopentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentenyl, cyclohexenyl, methylcyclopropyl, ethylcyclohexenyl, butenylcyclopentyl, and the like.

The term "substituted alkyl" represents an alkyl group as defined above wherein the substitutents are independently selected from halo, cyano, nitro, trihalomethyl, carbamoyl, hydroxy, oxo, COR_5, C_1-C_6alkyl, C_1-C_6alkyloxy, aryloxy, arylC_1-C_6alkyloxy, thio, C_1-C_6alkylthio, arylthio, arylC_1-C_6alkylthio, NR_7R_8, C_1-C_6alkylamino, arylamino, arylC_1-C_6alkylamino, di(arylC_1-C_6alkyl)amino, C_1-C_6alkylcarbonyl, arylC_1-C_6alkylcarbonyl, C_1-C_6alkyl-carboxy, arylC_1-C_6alkylcarboxy, C_1-C_6alkylcarbonylamino, -C_1-C_6alkyl-aminoCOR_{11}, arylC_1-C_6alkylcarbonylamino, tetrahydrofuranyl, morpholinyl, piperazinyl, -$CONR_7R_8$, -C_1-C_6alkyl$CONR_7R_8$, or a saturated or partial saturated cyclic 5, 6 or 7 membered amine, imide or lactam; wherein R_{11} is hydroxy, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkyloxy, aryloxy, arylC_1-C_6alkyloxy and R_5 is defined as above or NR_7R_8, wherein R_7, R_8 are defined as above.

The term "saturated, partially saturated or aromatic cyclic, bicyclic or tricyclic ring system" represents but are not limit to aziridinyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, 2-imidazolinyl, imidazolidinyl, pyrazolyl, 2-pyrazolinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, morpholinyl, piperidinyl, thiomorpholinyl, piperazinyl, indolyl, isoindolyl, 1,2,3,4-tetrahydro-quinolinyl, 1,2,3,4-tetrahydro-isoquinolinyl, 1,2,3,4-tetrahydro-quinoxalinyl, indolinyl, indazolyl, benzimidazolyl, benzotriazolyl, purinyl, carbazolyl, acridinyl, phenothiazinyl, phenoxazinyl, iminodibenzyl, iminostilbenyl.

The term "alkyloxy" (e.g. methoxy, ethoxy, propyloxy, allyloxy, cyclohexyloxy) represents an "alkyl" group as defined above having the indicated number of carbon atoms attached through an oxygen bridge. The term "alkyloxyalkyl" represents an

"alkyloxy" group attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term "alkyloxyalkyloxy" represents an "alkyloxyalkyl" group attached through an oxygen atom as defined above having the indicated number of carbon atoms.

The term "aryloxy" (e.g. phenoxy, naphthyloxy and the like) represents an aryl group as defined below attached through an oxygen bridge.

The term "arylalkyloxy" (e.g. phenethyloxy, naphthylmethyloxy and the like) represents an "arylalkyl" group as defined below attached through an oxygen bridge.

The term "arylalkyloxyalkyl" represents an "arylalkyloxy" group as defined above attached through an "alkyl" group defined above having the indicated number of carbon atoms.

The term "arylthio" (e.g. phenylthio, naphthylthio and the like) represents an "aryl" group as defined below attached through an sulfur bridge.

The term "alkyloxycarbonyl" (e.g. methylformiat, ethylformiat and the like) represents an "alkyloxy" group as defined above attached through a carbonyl group.

The term "aryloxycarbonyl" (e.g. phenylformiat, 2-thiazolylformiat and the like) represents an "aryloxy" group as defined above attached through a carbonyl group.

The term "arylalkyloxycarbonyl" (e.g. benzylformiat, phenyletylformiat and the like) represents an "arylalkyloxy" group as defined above attached through a carbonyl group.

The term "alkyloxycarbonylalkyl" represents an "alkyloxycarbonyl" group as defined above attached through an "alkyl" group as defined above having the indicated number of carbon atoms.

The term "arylalkyloxycarbonylalkyl" represents an "arylalkyloxycarbonyl" group as defined above attached through an "alkyl" group as defined above having the indicated number of carbon atoms.

The term "alkylthio" (e.g. methylthio, ethylthio, propylthio, cyclohexenylthio and the like) represents an "alkyl" group as defined above having the indicated number of carbon atoms attached through a sulfur bridge.

The term "arylalkylthio" (e.g. phenylmethylthio, phenylethylthio, and the like) represents an "arylalkyl" group as defined above having the indicated number of carbon atoms attached through a sulfur bridge.

The term "alkylthioalkyl" represents an "alkylthio" group attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term "arylalkylthioalkyl" represents an "arylalkylthio" group attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term "alkylamino" (e.g. methylamino, diethylamino, butylamino, N-propyl-N-hexylamino, (2-cyclopentyl)propylamino, hexenylamino, pyrrolidinyl, piperidinyl and the like) represents one or two "alkyl" groups as defined above having the indicated number of carbon atoms attached through an amine bridge. The two alkyl groups may be taken together with the nitrogen to which they are attached forming a saturated, partially saturated or aromatic cyclic, bicyclic or tricyclic ring system containing 3 to 14 carbon atoms and from 0 to 3 additional heteroatoms selected from nitrogen, oxygen or sulfur, the ring system can optionally be substituted with at least one C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, oxo, C_1-C_6alkyloxy, arylC_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, NR_9R_{10} or C_1-C_6alkylaminoC_1-C_6alkyl, wherein R_9 and R_{10} are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, arylcarbonyl, arylC_1-C_6alkylcarbonyl, C_1-C_6alkylcarboxy or arylC_1-C_6alkylcarboxy; wherein the alkyl and aryl groups are optionally substituted; or the two alkyl groups may form a saturated or partial saturated cyclic 5, 6 or 7 membered amine, imide or lactam;

The term "arylalkylamino" (e.g. benzylamino, diphenylethylamino and the like) represents one or two "arylalkyl" groups as defined above having the indicated number of carbon atoms attached through an amine bridge. The two "arylalkyl" groups may be taken together with the nitrogen to which they are attached forming a saturated, partially saturated or aromatic cyclic, bicyclic or tricyclic ring system containing 3 to 14 carbon atoms and 0 to 3 additional heteroatoms selected from nitrogen, oxygen or sulfur, the ring system can optionally be substituted with at least one C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, oxo, C_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, NR_9R_{10}, C_1-

C_6alkylaminoC_1-C_6alkyl substituent wherein the alkyl and aryl groups are optionally substituted as defined in the definition section and R_9 and R_{10} are defined as above.

The term "alkylaminoalkyl" represents an "alkylamino" group attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term "arylalkylaminoalkyl" represents an "arylalkylamino" group attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term "arylalkyl" (e.g. benzyl, phenylethyl) represents an "aryl" group as defined below attached through an alkyl having the indicated number of carbon atoms or substituted alkyl group as defined above.

The term "alkylcarbonyl" (e.g. cyclooctylcarbonyl, pentylcarbonyl, 3-hexenylcarbonyl) represents an "alkyl" group as defined above having the indicated number of carbon atoms attached through a carbonyl group.

The term "arylcarbonyl" (benzoyl) represents an "aryl" group as defined above attached through a carbonyl group.

The term "arylalkylcarbonyl" (e.g. phenylcyclopropylcarbonyl, phenylethylcarbonyl and the like) represents an "arylalkyl" group as defined above having the indicated number of carbon atoms attached through a carbonyl group.

The term "alkylcarbonylalkyl" represents an "alkylcarbonyl" group attached through an "alkyl" group as defined above having the indicated number of carbon atoms.

The term "arylalkylcarbonylalkyl" represents an "arylalkylcarbonyl" group attached through an alkyl group as defined above having the indicated number of carbon atoms.

The term "alkylcarboxy" (e.g. heptylcarboxy, cyclopropylcarboxy, 3-pentenylcarboxy) represents an "alkylcarbonyl" group as defined above wherein the carbonyl is in turn attached through an oxygen bridge.

The term "arylcarboxyalkyl" (e.g. phenylcarboxymethyl) represents an "arylcarbonyl" group defined above wherein the carbonyl is in turn attached through an oxygen bridge to an alkyl chain having the indicated number of carbon atoms.

The term "arylalkylcarboxy" (e.g. benzylcarboxy, phenylcyclopropylcarboxy and the like) represents an "arylalkylcarbonyl" group as defined above wherein the carbonyl is in turn attached through an oxygen bridge.

The term "alkylcarboxyalkyl" represents an "alkylcarboxy" group attached through an "alkyl" group as defined above having the indicated number of carbon atoms.

The term "arylalkylcarboxyalkyl" represents an "arylalkylcarboxy" group attached through an "alkyl" group as defined above having the indicated number of carbon atoms.

The term "alkylcarbonylamino" (e.g. hexylcarbonylamino, cyclopentylcarbonylaminomethyl, methylcarbonylaminophenyl) represents an "alkylcarbonyl" group as defined above wherein the carbonyl is in turn attached through the nitrogen atom of an amino group. The nitrogen atom may itself be substituted with an alkyl or aryl group.

The term "arylalkylcarbonylamino" (e.g. benzylcarbonylamino and the like) represents an "arylalkylcarbonyl" group as defined above wherein the carbonyl is in turn attached through the nitrogen atom of an amino group. The nitrogen atom may itself be substituted with an alkyl or aryl group.

The term "alkylcarbonylaminoalkyl" represents an "alkylcarbonylamino" group attached through an "alkyl" group as defined above having the indicated number of carbon atoms. The nitrogen atom may itself be substituted with an alkyl or aryl group.

The term "arylalkylcarbonylaminoalkyl" represents an "arylalkylcarbonylamino" group attached through an "alkyl" group as defined above having the indicated number of carbon atoms. The nitrogen atom may itself be substituted with an alkyl or aryl group.

The term "alkylcarbonylaminoalkylcarbonyl" represents an alkylcarbonylaminoalkyl group attached through a carbonyl group. The nitrogen atom may be further substituted with an "alkyl" or "aryl" group.

The term "aryl" represents an unsubstituted, mono-, di- or trisubstituted monocyclic, polycyclic, biaryl and heterocyclic aromatic groups covalently attached at any ring

position capable of forming a stable covalent bond, certain preferred points of attachment being apparent to those skilled in the art (e.g., 3-indolyl, 4-imidazolyl). The aryl substituents are independently selected from the group consisting of halo, nitro, cyano, trihalomethyl, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, COR_5, C_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, aryloxy, arylC_1-C_6alkyloxy, arylC_1-C_6alkyloxyC_1-C_6alkyl, thio, C_1-C_6alkylthio, C_1-C_6alkylthioC_1-C_6alkyl, arylthio, arylC_1-C_6alkylthio, arylC_1-C_6alkylthioC_1-C_6alkyl, NR_8R_9, C_1-C_6alkylamino, C_1-C_6alkylaminoC_1-C_6alkyl, arylamino, arylC_1-C_6alkylamino, arylC_1-C_6alkylaminoC_1-C_6alkyl, di(arylC_1-C_6alkyl)aminoC_1-C_6alkyl, C_1-C_6alkylcarbonyl, C_1-C_6alkylcarbonylC_1-C_6alkyl, arylC_1-C_6alkylcarbonyl, arylC_1-C_6alkylcarbonylC_1-C_6alkyl, C_1-C_6alkylcarboxy, C_1-C_6alkylcarboxyC_1-C_6alkyl, arylC_1-C_6alkylcarboxy, arylC_1-C_6alkylcarboxyC_1-C_6alkyl, carboxyC_1-C_6alkyloxy, C_1-C_6alkylcarbonylamino, C_1-C_6alkylcarbonyl-aminoC_1-C_6alkyl, -carbonylNR_7C_1-C_6alkylCOR_{11}, arylC_1-C_6alkylcarbonylamino, arylC_1-C_6alkylcarbonylaminoC_1-C_6alkyl, -$CONR_8R_9$, or -C_1-C_6alkyl-$CONR_8R_9$; wherein R_7, R_8, R_9, and R_{11} are defined as above and the alkyl and aryl groups are optionally substituted as defined in the definition section;

The definition of aryl includes but is not limited to phenyl, biphenyl, indenyl, fluorenyl, naphthyl (1-naphthyl, 2-naphthyl), pyrrolyl (2-pyrrolyl), pyrazolyl (3-pyrazolyl), imidazolyl (1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), triazolyl (1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl), oxazolyl (2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isoxazolyl (3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), thiazolyl (2-thiazolyl, 4-thiazolyl, 5-thiazolyl), thiophenyl (2-thiophenyl, 3-thiophenyl, 4-thiophenyl, 5-thiophenyl), furanyl (2-furanyl, 3-furanyl, 4-furanyl, 5-furanyl), pyridyl (2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl), 5-tetrazolyl, pyrimidinyl (2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyrazinyl, pyridazinyl (3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl), quinolyl (2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 8-quinolyl), isoquinolyl (1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-isoquinolyl, 7-isoquinolyl, 8-isoquinolyl), benzo[b]furanyl (2-benzo[b]furanyl, 3-benzo[b]furanyl, 4-benzo[b]furanyl, 5-benzo[b]furanyl, 6-benzo[b]furanyl, 7-benzo[b]furanyl), 2,3-dihydro-benzo[b]furanyl (2-(2,3-dihydro-

benzo[b]furanyl), 3-(2,3-dihydro-benzo[b]furanyl), 4-(2,3-dihydro-benzo[b]furanyl), 5-(2,3-dihydro-benzo-[b]furanyl), 6-(2,3-dihydro-benzo-[b]furanyl), 7-(2,3-dihydro-benzo[b]furanyl)), benzo[b]thiophenyl (2-benzo[b]thiophenyl, 3-benzo[b]thiophenyl, 4-benzo[b]thiophenyl, 5-benzo[b]thiophenyl, 6-benzo[b]thiophenyl, 7-benzo[b]thiophenyl), 2,3-dihydro-benzo[b]-thiophenyl (2-(2,3-dihydro-benzo[b]thiophenyl), 3-(2,3-dihydro-benzo[b]-thiophenyl), 4-(2,3-dihydro-benzo[b]thiophenyl), 5-(2,3-dihydro-benzo[b]-thiophenyl), 6-(2,3-dihydro-benzo[b]thiophenyl), 7-(2,3-dihydro-benzo[b]-thiophenyl)), 4,5,6,7-tetrahydro-benzo[b]thiophenyl (2-(4,5,6,7-tetrahydro-benzo-[b]thiophenyl), 3-(4,5,6,7-tetrahydro-benzo-[b]thiophenyl), 4-(4,5,6,7-tetrahydro-benzo[b]thiophenyl), 5-(4,5,6,7-tetrahydro-benzo-[b]thiophenyl), 6-(4,5,6,7-tetrahydro-benzo-[b]thiophenyl), 7-(4,5,6,7-tetrahydro-benzo[b]thiophenyl)), 4,5,6,7-tetrahydro-thieno[2,3-c]pyridyl (4-(4,5,6,7-tetrahydro-thieno[2,3-c]pyridyl), 5-(4,5,6,7-tetrahydro-thieno[2,3-c]pyridyl), 6-(4,5,6,7-tetrahydro-thieno[2,3-c]pyridyl), 7-(4,5,6,7-tetrahydro-thieno[2,3-c]pyridyl)), indolyl (1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl), isoindolyl (1-isoindolyl, 2-isoindolyl, 3-isoindolyl, 4-isoindolyl, 5-isoindolyl, 6-isoindolyl, 7-isoindolyl), 1,3-dihydro-isoindolyl (1-(1,3-dihydro-isoindolyl), 2-(1,3-dihydro-isoindolyl), 3-(1,3-dihydro-isoindolyl), 4-(1,3-dihydro-isoindolyl), 5-(1,3-dihydro-isoindolyl), 6-(1,3-dihydro-isoindolyl), 7-(1,3-dihydro-isoindolyl)), indazole (1-indazolyl, 3-indazolyl, 4-indazolyl, 5-indazolyl, 6-indazolyl, 7-indazolyl), benzimidazolyl (1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, 5-benzimidazolyl, 6-benzimidazolyl, 7-benzimidazolyl, 8-benzimidazolyl), benzoxazolyl (1-benz-oxazolyl, 2-benzoxazolyl), benzothiazolyl (1-benzothiazolyl, 2-benzo-thiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, 7-benzothiazolyl), carbazolyl (1-carbazolyl, 2-carbazolyl, 3-carbazolyl, 4-carbazolyl), 5H-dibenz[b,f]azepine (5H-dibenz[b,f]azepin-1-yl, 5H-dibenz-[b,f]azepine-2-yl, 5H-dibenz[b,f]azepine-3-yl, 5H-dibenz-[b,f]azepine-4-yl, 5H-dibenz[b,f]-azepine-5-yl), 10,11-dihydro-5H-dibenz[b,f]azepine (10,11-dihydro-5H-dibenz[b,f]azepine-1-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-2-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-3-yl, 10,11-dihydro-5H-dibenz-[b,f]azepine-4-yl, 10,11-dihydro-5H-dibenz[b,f]azepine-5-yl), piperidinyl (2-piperidinyl, 3-piperidinyl, 4-piperidinyl), pyrrolidinyl (1-pyrrolidinyl, 2-pyrrolidinyl, 3-

pyrrolidinyl), phenylpyridyl (2-phenyl-pyridyl, 3-phenyl-pyridyl, 4-phenylpyridyl), phenylpyrimidinyl (2-phenylpyrimidinyl, 4-phenyl-pyrimidinyl, 5-phenylpyrimidinyl, 6-phenylpyrimidinyl), phenylpyrazinyl, phenylpyridazinyl (3-phenylpyridazinyl, 4-phenylpyridazinyl, 5-phenyl-pyridazinyl).

The term “arylcarbonyl” (e.g. 2-thiophenylcarbonyl, 3-methoxy-anthrylcarbonyl, oxazolylcarbonyl) represents an “aryl” group as defined above attached through a carbonyl group.

The term "arylalkylcarbonyl" (e.g. (2,3-dimethoxyphenyl)-propylcarbonyl, (2-chloronaphthyl)pentenylcarbonyl, imidazolylcyclo-pentylcarbonyl) represents an “arylalkyl” group as defined above wherein the “alkyl” group is in turn attached through a carbonyl.

The compounds of the present invention have asymmetric centers and may occur as racemates, racemic mixtures, and as individual enantiomers or diastereoisomers, with all isomeric forms being included in the present invention as well as mixtures thereof.

Pharmaceutically acceptable salts of the compounds of formula 1, where a basic or acidic group is present in the structure, are also included within the scope of this invention. When an acidic substituent is present, such as -COOH, 5-tetrazolyl or -$P(O)(OH)_2$, there can be formed the ammonium, morpholinium, sodium, potassium, barium, calcium salt, and the like, for use as the dosage form. When a basic group is present, such as amino or a basic heteroaryl radical, such as pyridyl, an acidic salt, such as hydrochloride, hydrobromide, phosphate, sulfate, trifluoroacetate, trichloroacetate, acetate, oxalate, maleate, pyruvate, malonate, succinate, citrate, tartarate, fumarate, mandelate, benzoate, cinnamate, methanesulfonate, ethane sulfonate, picrate and the like, and include acids related to the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2 (1977) and incorporated herein by reference, can be used as the dosage form.

Also, in the case of the -COOH or -$P(O)(OH)_2$ being present, pharmaceutically acceptable esters can be employed, e.g., methyl, tert-butyl, pivaloyloxymethyl, and the

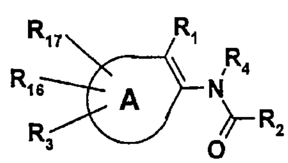
like, and those esters known in the art for modifying solubility or hydrolysis characteristics for use as sustained release or prodrug formulations.

In addition, some of the compounds of the instant invention may form solvates with water or common organic solvents. Such solvates are encompassed within the scope of the invention.

The term "therapeutically effective amount" shall mean that amount of drug or pharmaceutical agent that will elicit the biological or medical response of a tissue, system, animal, or human that is being sought by a researcher, veterinarian, medical doctor or other.

PREFERRED EMBODIMENTS OF THE INVENTION

Compounds of Formula 1a are preferred compounds of the invention

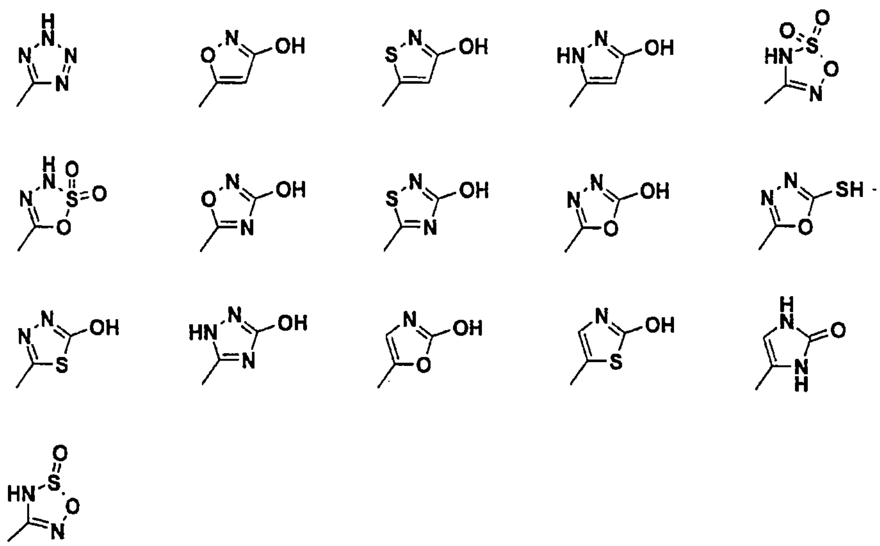


Formula 1a

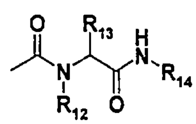
wherein

A is together with the double bond in Formula 1a furanyl, thiophenyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, furazanyl or 1,2,3-triazolyl;

R_1 is COR_5, OR_6, CF_3, nitro, cyano, SO_3H, $SO_2NR_7R_8$, $PO(OH)_2$, $CH_2PO(OH)_2$, $CHFPO(OH)_2$, $CF_2PO(OH)_2$, $C(=NH)NH_2$, NR_7R_8 or selected from the following 5-membered heterocycles:

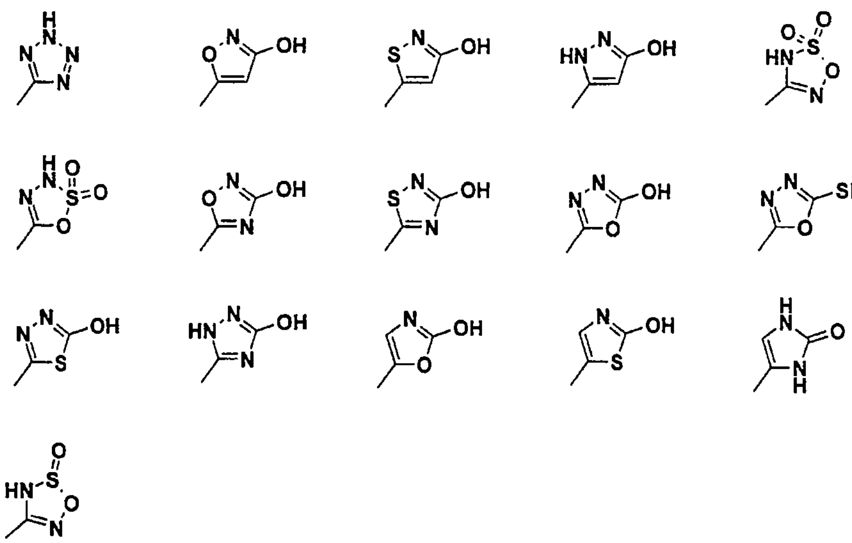


or R_1 is

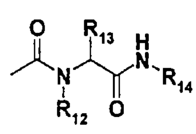


wherein R_{12}, R_{13}, and R_{14} are independently hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl and the alkyl and aryl groups are optionally substituted;

R_2 is COR_5, OR_6, CF_3, nitro, cyano, SO_3H, $SO_2NR_7R_8$, $PO(OH)_2$, $CH_2PO(OH)_2$, $CHFPO(OH)_2$, $CF_2PO(OH)_2$, $C(=NH)NH_2$, NR_7R_8 , or selected from the following 5-membered heterocycles:



R_3, R_{16} and R_{17} are independently hydrogen, halo, nitro, cyano, trihalomethyl, C_1-C_6alkyl, aryl, arylC_1-C_6-alkyl, hydroxy, carboxy, carboxyC_1-C_6alkyl, C_1-C_6alkyloxy-carbonyl, aryloxycarbonyl, arylC_1-C_6alkyloxycarbonyl, C_1-C_6alkyloxy, C_1-C_6alkyl-oxyC_1-C_6alkyl, aryloxy, arylC_1-C_6alkyloxy, arylC_1-C_6alkyl-oxyC_1-C_6alkyl, thio, C_1-C_6alkylthio, C_1-C_6alkylthioC_1-C_6alkyl, arylthio, arylC_1-C_6alkylthio, arylC_1-C_6alkylthioC_1-C_6alkyl, NR_7R_8, C_1-C_6alkyl-aminoC_1-C_6alkyl, arylC_1-C_6alkylaminoC_1-C_6alkyl, di(arylC_1-C_6alkyl)-aminoC_1-C_6alkyl, C_1-C_6alkylcarbonyl, C_1-C_6alkylcarbonylC_1-C_6alkyl, arylC_1-C_6alkylcarbonyl, arylC_1-C_6alkylcarbonylC_1-C_6alkyl, C_1-C_6alkyl-carboxy, C_1-C_6alkyl-carboxyC_1-C_6-alkyl, arylcarboxy, arylC_1-C_6alkyl-carboxy, arylC_1-C_6alkylcarboxyC_1-C_6alkyl, C_1-C_6alkylcarbonylamino, C_1-C_6alkylcarbonyl-aminoC_1-C_6alkyl, -carbonylNR_7C_1-C_6alkylCOR_{11}, arylC_1-C_6alkyl-carbonylamino, arylC_1-C_6alkylcarbonylaminoC_1-C_6alkyl, $CONR_7R_8$, or C_1-C_6alkyl$CONR_7R_8$ wherein the alkyl and aryl groups are optionally substituted and R_{11} is NR_7R_8, or C_1-C_6alkylNR_7R_8; or R_3 is



wherein R_{12}, R_{13}, and R_{14} are independently hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl and the alkyl and aryl groups are optionally substituted;

R_4 is hydrogen, hydroxy, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, NR_7R_8, C_1-C_6alkyloxy; wherein the alkyl and aryl groups are optionally substituted;

R_5 is hydroxy, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, CF_3, NR_7R_8; wherein the alkyl and aryl groups are optionally substituted;

R_6 is hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl; wherein the alkyl and aryl groups are optionally substituted;

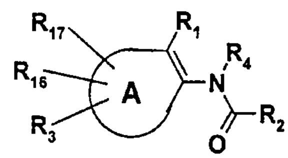
R_7 and R_8 are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkyl-carbonyl, arylcarbonyl, arylC_1-C_6alkyl-carbonyl, C_1-C_6alkyl-carboxy or arylC_1-C_6alkylcarboxy wherein the alkyl and aryl groups are optionally substituted; or R_7 and R_8 are taken together with the nitrogen to which they are attached forming a cyclic or bicyclic system containing 3 to 11 carbon atoms and 0 to 2 additional heteroatoms selected from nitrogen, oxygen or sulfur, the ring system can optionally be substituted with at least one C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, C_1-C_6alkyloxy, arylC_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, NR_9R_{10} or C_1-C_6alkylamino-C_1-C_6alkyl, wherein R_9 and R_{10} are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, arylcarbonyl, arylC_1-C_6alkylcarbonyl, C_1-C_6alkyl-carboxy or arylC_1-C_6alkylcarboxy; wherein the alkyl and aryl groups are optionally substituted; or

R_7 and R_8 are independently a saturated or partial saturated cyclic 5, 6 or 7 membered amine or lactam;

Further, preferred compounds of the invention are compounds wherein R_{16} and R_{17} are hydrogen.

The invention will in its broadest aspect cover the following compounds:

of Formula 1:

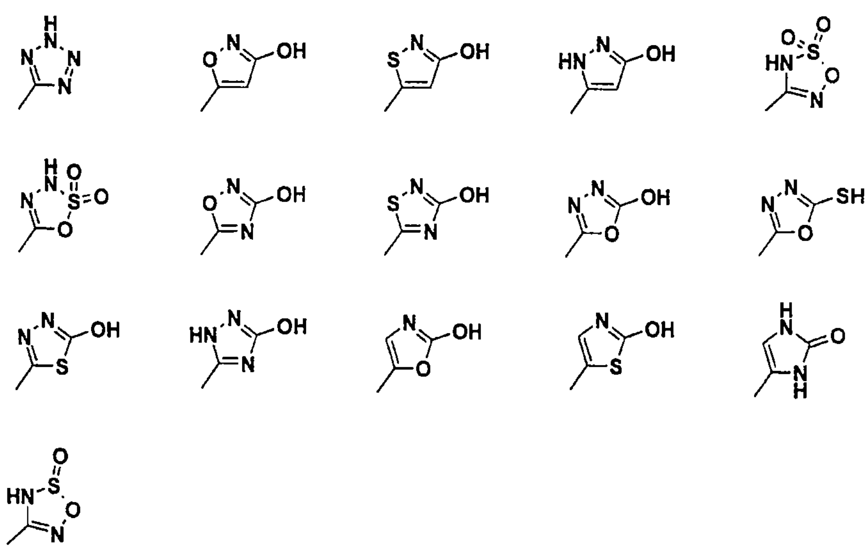


Formula 1

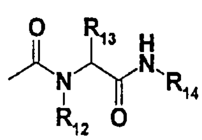
wherein

A is together with the double bond in Formula 1 is aryl;

R_1 is hydrogen, COR_5, OR_6, CF_3, nitro, cyano, CH_2OH, SO_3H, $SO_2NR_7R_8$, $PO(OH)_2$, $CH_2PO(OH)_2$, $CHFPO(OH)_2$, $CF_2PO(OH)_2$, $C(=NH)NH_2$, NR_7R_8; or selected from the following 5-membered heterocycles:

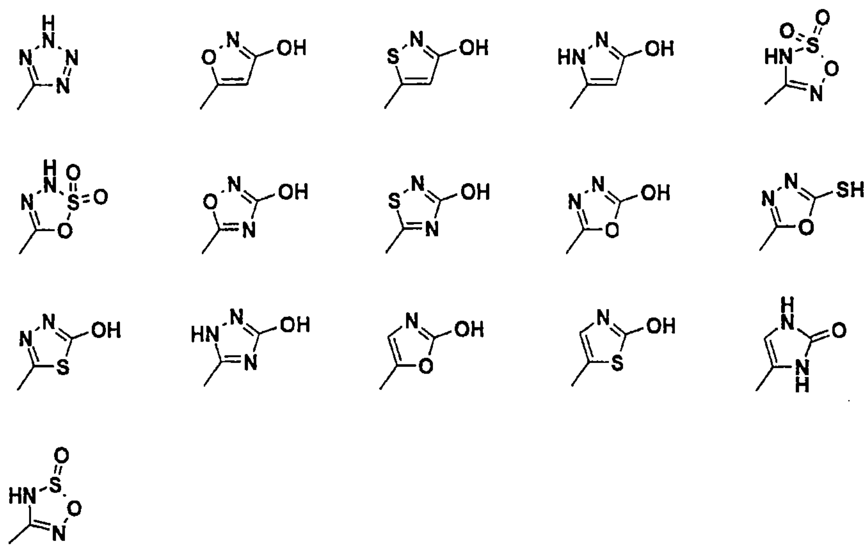


or R_1 is



wherein R_{12}, R_{13}, and R_{14} are independently hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl and the alkyl and aryl groups are optionally substituted;

R_2 is COR_5, OR_6, CF_3, nitro, cyano, SO_3H, $SO_2NR_7R_8$, $PO(OH)_2$, $CH_2PO(OH)_2$, $CHFPO(OH)_2$, $CF_2PO(OH)_2$, $C(=NH)NH_2$, NR_7R_8; or selected from the following 5-membered heterocycles:



R_3, R_{16} and R_{17} are independently hydrogen, halo, nitro, cyano, trihalomethyl, C_1-C_6alkyl, aryl, arylC_1-C_6-alkyl, hydroxy, oxo, carboxy, carboxyC_1-C_6alkyl, C_1-C_6alkyloxycarbonyl, aryloxycarbonyl, arylC_1-C_6alkyloxycarbonyl, C_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, aryloxy, arylC_1-C_6alkyloxy, arylC_1-C_6alkyloxyC_1-C_6alkyl, thio, C_1-C_6alkylthio, C_1-C_6alkylthioC_1-C_6alkyl, arylthio, arylC_1-C_6alkylthio, arylC_1-C_6alkylthioC_1-C_6alkyl, NR_7R_8, C_1-C_6alkylaminoC_1-C_6alkyl, arylC_1-C_6alkylaminoC_1-C_6alkyl, di(arylC_1-C_6alkyl)aminoC_1-C_6alkyl, C_1-C_6alkylcarbonyl, C_1-C_6alkylcarbonyl-C_1-C_6alkyl, arylC_1-C_6alkylcarbonyl, arylC_1-C_6alkylcarbonylC_1-C_6alkyl, C_1-C_6alkylcarboxy, C_1-C_6alkylcarboxyC_1-C_6alkyl, arylcarboxy, arylcarboxyC_1-C_6alkyl, arylC_1-C_6alkylcarboxy, arylC_1-C_6alkylcarboxyC_1-C_6alkyl, C_1-C_6alkylcarbonylamino, C_1-C_6alkylcarbonylaminoC_1-C_6alkyl, -carbonylNR_7C_1-C_6alkylCOR_{11}, arylC_1-C_6alkylcarbonylamino, arylC_1-C_6alkylcarbonylaminoC_1-C_6alkyl, $CONR_7R_8$, or C_1-C_6alkyl$CONR_7R_8$ wherein the alkyl and aryl groups are optionally substituted and R_{11} is NR_7R_8, or C_1-C_6alkylNR_7R_8; or, when R_{16} and R_{17} are hydrogen, R_3 is

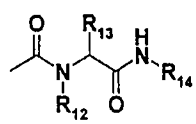
A-B-C-D-C_1-C_6alkyl, wherein

A is C_1-C_8alkyl, aryl or arylC$_1$-C_6alkyl;

B is amino, thio, SO, SO_2 or oxo;

C is C_1-C_8alkyl, amino;

D is a chemical bond, amino or C_1-C_8alkyl wherein the alkyl and aryl groups are optionally substituted; or



wherein R_{12}, R_{13}, and R_{14} are independently hydrogen, C_1-C_6alkyl, aryl, arylC$_1$-C_6alkyl and the alkyl and aryl groups are optionally substituted;

R_4 is hydrogen, hydroxy, C_1-C_6alkyl, aryl, arylC$_1$-C_6alkyl, NR_7R_8, C_1-C_6alkyloxy; wherein the alkyl and aryl groups are optionally substituted;

R_5 is hydroxy, C_1-C_6alkyl, aryl, arylC$_1$-C_6alkyl, C_1-C_6alkyloxy, C_1-C_6alkyl-oxyC$_1$-C_6alkyloxy, aryloxy, arylC$_1$-C_6alkyloxy, CF_3, NR_7R_8; wherein the alkyl and aryl groups are optionally substituted;

R_6 is hydrogen, C_1-C_6alkyl, aryl, arylC$_1$-C_6alkyl; wherein the alkyl and aryl groups are optionally substituted;

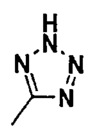
R_7 and R_8 are independently selected from hydrogen, C_1-C_6alkyl, adamantyl, aryl, arylC$_1$-C_6alkyl, C_1-C_6alkylcarbonyl, arylcarbonyl, arylC$_1$-C_6alkylcarbonyl, C_1-C_6alkylcarboxy or arylC$_1$-C_6alkylcarboxy wherein the alkyl and aryl groups are optionally substituted; or

R_7 and R_8 are taken together with the nitrogen to which they are attached forming a saturated, partially saturated or aromatic cyclic, bicyclic or tricyclic ring system containing 3 to 14 carbon atoms and from 0 to 3 additional heteroatoms selected from nitrogen, oxygen or sulfur, the ring system can optionally be substituted with at least one C_1-C_6alkyl, aryl, arylC$_1$-C_6alkyl, hydroxy, oxo, C_1-C_6alkyloxy, arylC$_1$-C_6alkyloxy,

C_1-C_6alkyloxyC_1-C_6alkyl, NR_9R_{10} or C_1-C_6alkylaminoC_1-C_6alkyl, wherein R_9 and R_{10} are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, arylcarbonyl, arylC_1-C_6alkylcarbonyl, C_1-C_6alkylcarboxy or arylC_1-C_6alkylcarboxy; wherein the alkyl and aryl groups are optionally substituted; or R_7 and R_8 are independently a saturated or partial saturated cyclic 5, 6 or 7 membered amine, imide or lactam;

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

Particular preferred compounds of the invention are those compounds of formula I wherein R_1 is 5-tetrazolyl, i.e.



or COR_5 and R_2 is COR_5.
In particular, preferred compounds are those wherein R_5 is OH and R_4 is hydrogen.

The following compounds are preferred:

2-Methyl-4-(oxalyl-amino)-1H-pyrrole-3-carboxylic acid;
1-Benzyl-3-(oxalyl-amino)-1H-pyrazole-4-carboxylic acid;
3-(Oxalyl-amino)-1H-pyrazole-4-carboxylic acid;
4-Cyclohexyl-2-(oxalyl-amino)-thiophene-3-carboxylic acid;
2-(Oxalyl-amino)-thiophene-3-carboxylic acid;
2-(Oxalyl-amino)-4-phenyl-thiophene-3-carboxylic acid;
3-(Oxalyl-amino)-thiophene-2-carboxylic acid;
3-(Oxalyl-amino)-5-phenyl-thiophene-2-carboxylic acid;
4-(Oxalyl-amino)-[2,3]-bithiophenyl-5-carboxylic acid;

4-Methyl-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

2-(Oxalyl-amino)-5-phenyl-thiophene-3-carboxylic acid;

5-(4-Chloro-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(4-Fluoro-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(4-Isobutyl-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

3-(Oxalyl-amino)-5-(4-phenoxy-phenyl)-thiophene-2-carboxylic acid;

5-(4-Benzyloxy-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(4-(4-Methoxy-phenoxy)-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(4-Hydroxy-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-(phenyl-methyl)thiophene-3-carboxylic acid;

5-(2-(4-Chloro-phenyl)-ethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(Naphthalen-2-yl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3-Nitro-phenyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(2-Fluoro-phenyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3-Chloro-phenyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(2,4-Dichloro-phenyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(4-Bromo-phenyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-Ethyl-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-Methyl-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3-Methyl-phenyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-Dibenzofuran-2-yl-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3,4-Dimethoxy-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(3-Methoxy-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(3,5-Dimethoxy-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(3-Nitro-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(3-Amino-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(4-Methoxy-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(4-(2-(2-Methoxy-phenyl)-2-oxo-ethoxy)-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(4-Carboxymethoxy-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(4-(4-Fluoro-benzyloxy)-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(4-Amino-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(4-Carbamoylmethoxy-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-((2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acetylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3-Ethoxycarbonylmethyl-ureidomethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3-tert-Butyl-ureidomethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-((3-Ethyl-ureido)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3-(2-Nitro-phenyl)-ureidomethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3-(3-Methoxy-phenyl)-ureidomethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3-(3-Acetyl-phenyl)-ureidomethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-((3-propyl-ureido)-methyl)-thiophene-3-carboxylic acid;

5-(3-(3-Bromo-phenyl)-ureidomethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3-(2,6-Diisopropyl-phenyl)-ureidomethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3-(4-Nitro-phenyl)-ureidomethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-((3-Naphthalen-1-yl-ureido)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-((3-Biphenyl-2-yl-ureido)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3-(3,5-Bis-trifluoromethyl-phenyl)-ureidomethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-(3-(2-trifluoromethyl-phenyl)-ureidomethyl)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-(3-(3-trifluoromethyl-phenyl)-ureidomethyl)-thiophene-3-carboxylic acid;

5-(3-Isopropyl-ureidomethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-((3-Cyclohexyl-ureido)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3-(2-Methoxy-phenyl)-ureidomethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3-Benzyl-ureidomethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3-(2,4-Dimethoxy-phenyl)-ureidomethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-((3-Adamantan-1-yl-ureido)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-((3-phenyl-ureido)-methyl)-thiophene-3-carboxylic acid;

5-(3-(3-Nitro-phenyl)-ureidomethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-(3-(3,4,5-trimethoxy-phenyl)-ureidomethyl)-thiophene-3-carboxylic acid;

2-Oxalyl-amino-5-(3-(phenylsulfonyl)ureidomethyl)-thiophene-3-carboxylic acid;

2-Oxalyl-amino-5-(3-(2-methyl-phenylsulfonyl)ureidomethyl)-thiophene-3-carboxylic acid;

2-Oxalyl-amino-5-(3-(4-chloro-phenylsulfonyl)ureidomethyl)-thiophene-3-carboxylic acid;

5-((4-Bromo-phenoxycarbonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-((4-Fluoro-phenoxycarbonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-((2,2-Dimethyl-propoxycarbonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-((2-Nitro-phenoxycarbonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

2-Oxalyl-amino-5-(3-(4-methyl-phenylsulfonyl)ureidomethyl)-thiophene-3-carboxylic acid;

5-((2-Ethyl-hexyloxycarbonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(Benzyloxycarbonylamino-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-(propoxycarbonylamino-methyl)-thiophene-3-carboxylic acid;

5-(Isopropoxycarbonylamino-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-((4-Nitro-phenoxycarbonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-((4-Nitro-benzyloxycarbonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-((4-Methoxy-phenoxycarbonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(Octyloxycarbonylamino-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-(prop-2-ynyloxycarbonylamino-methyl)-thiophene-3-carboxylic acid;

5-(Ethoxycarbonylamino-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(Isobutoxycarbonylamino-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(Allyloxycarbonylamino-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(But-3-enyloxycarbonylamino-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-((4-Bromo-benzenesulfonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(Methoxycarbonylamino-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-(phenoxycarbonylamino-methyl)-thiophene-3-carboxylic acid;

5-((2-Nitro-phenylmethanesulfonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-((4-trifluoromethoxy-benzenesulfonylamino)-methyl)-thiophene-3-carboxylic acid;

5-((4-Chloro-benzenesulfonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-((propane-2-sulfonylamino)-methyl)-thiophene-3-carboxylic acid;

5-((4-Fluoro-benzenesulfonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(Methanesulfonylamino-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-((Naphthalene-1-sulfonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(Ethanesulfonylamino-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-((3-trifluoromethyl-benzenesulfonylamino)-methyl)-thiophene-3-carboxylic acid;

5-((4-Acetylamino-benzenesulfonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-((propane-1-sulfonylamino)-methyl)-thiophene-3-carboxylic acid;

5-(4-(tert-Butyl-benzenesulfonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-((2-Nitro-4-trifluoromethyl-benzenesulfonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-((2,2,2-trifluoro-ethanesulfonylamino)-methyl)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-((2-phenyl-ethenesulfonylamino)-methyl)-thiophene-3-carboxylic acid;

5-(Benzenesulfonylamino-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

PHARMACOLOGICAL METHODS

The compounds are evaluated for biological activity with a truncated form of PTP1B (corresponding to the first 321 amino acids), which was expressed in E. coli and purified to apparent homogeneity using published procedures well-known to those skilled in the art. The enzyme reactions are carried out using standard conditions essentially as described by Burke et al. (*Biochemistry* **35**; 15989-15996 (1996)). The assay conditions are as follows. Appropriate concentrations of the compounds of the invention are added to the reaction mixtures containing different concentrations of the substrate, *p*-nitrophenyl phosphate (range: 0.16 to 10 mM - final assay concentration). The buffer used was 100 mM sodium acetate pH 5.5, 50 mM sodium chloride, 0.1 % (w/v) bovine serum albumin and 5 mM dithiothreitol (total volume 100 ml). The reaction was started by addition of the enzyme and carried out in microtiter plates at 25 °C for 60 minutes. The reactions are stopped by addition of NaOH. The enzyme activity was determined by measurement of the absorbance at 405 nm with appropriate corrections for absorbance at 405 nm of the compounds and *p*-nitrophenyl phosphate. The data are analyzed using nonlinear regression fit to classical Michaelis Menten enzyme kinetic models. Inhibition is expressed as K_i values in μM. The results of representative experiments are shown in Table 1

Table 1

Inhibition of classical PTP1B by compounds of the invention

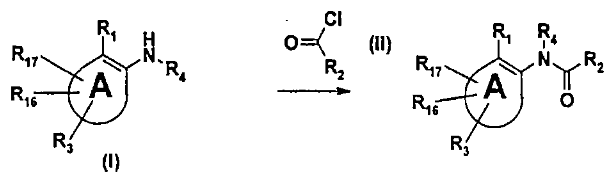
Example no.	PTP1B K_i values (μM)
1	200
4	100

Further, the compounds are evaluated for biological activity as regards their effect as inhibitors of PTPα in essentially the same way as described for inhibition of PTP1B. Derived from their activity as evaluated above the compounds of the invention may be useful in the treatment of diseases selected from the group consisting of type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance and obesity. Furthermore, derived from their activity as evaluated above, the compounds of the invention may be useful in the treatment of diseases selected from the group consisting of immune dysfunctions including autoimmunity, diseases with dysfunctions of the coagulation system, allergic diseases including asthma, osteoporosis, proliferative disorders including cancer and psoriasis, diseases with decreased or increased synthesis or effects of growth hormone, diseases with decreased or increased synthesis of hormones or cytokines that regulate the release of/or response to growth hormone, diseases of the brain including Alzheimer's disease and schizophrenia, and infectious diseases.

THE SYNTHESIS OF THE COMPOUNDS

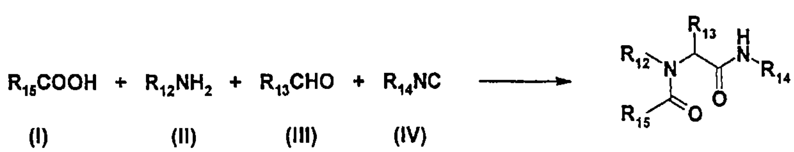
In accordance with one aspect of the invention, the compounds of the invention are prepared as illustrated in the following reaction scheme:

Method A

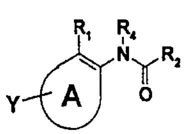


By allowing an amino substituted aryl or heteroaryl (I) to react with an acid chloride of formula (II), wherein A, R_1, R_2, R_3, R_4, R_{16} and R_{17} are defined as above.

Method B



By allowing a carboxylic acid (I), a primary amine (II) and an aldehyde (III) to react with a isocyanide (IV) wherein R_{12}, R_{13}, R_{14}, and R_{15} are independently selected from the group consisting of hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl as defined above and the alkyl and aryl groups are optionally substituted as defined above; or R_{12}, R_{13}, R_{14}, and R_{15} are independently selected from



wherein Y indicates attachment point for R_{12}, R_{13}, R_{14}, and R_{15} and A, R_1 R_2 and R_4 are defined as above.

In a preferred method, the above described four component Ugi reaction can be carried out by attaching any one of the components to a solid support. Hence, the synthesis can be accomplished in a combinatorial chemistry fashion.

General procedure for the Preparation of Acetoxymethyl Esters (C.Schultz et al, The Journal of Biological Chemistry, **1993**, 268, 6316-6322.): A carboxylic acid (1 equivalent) was suspended in dry acetonitrile (2 ml per 0.1 mmol). Diisopropyl amine (3.0 equivalents) was added followed by bromomethyl acetate (1.5 equivalents). The mixture was stirred under nitrogen overnight at room temperature. Acetonitrile was removed under reduced pressure to yield an oil which was diluted in ethylacetate and washed water (3 x). The organic layer was dried over anhydrous magnesium sulfate. Filtration followed by solvent removal under reduced pressure afforded a crude oil. The product was purified by column chromatography on silica gel, using an appropriate solvent system.

The present invention also has the objective of providing suitable topical, oral, and parenteral pharmaceutical formulations for use in the novel methods of treatment of the present invention. The compounds of the present invention may be administered orally as tablets, aqueous or oily suspensions, lozenges, troches, powders, granules, emulsions, capsules, syrups or elixirs. The composition for oral use may contain one or more agents selected from the group of sweetening agents, flavouring agents, colouring agents and preserving agents in order to produce pharmaceutically elegant and palatable preparations. The tablets contain the acting ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be, for example, (1) inert diluents, such as calcium carbonate, lactose, calcium phosphate or sodium phosphate; (2) granulating and disintegrating agents, such as corn starch or alginic acid; (3) binding agents, such as starch, gelatine or acacia; and (4) lubricating agents, such as magnesium stearate, stearic acid or talc. These tablets may be uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. Coating may also be performed using techniques described in the U.S. Pat-

ent Nos. 4,256,108; 4,160,452; and 4,265,874 to form osmotic therapeutic tablets for control release.

Formulations for oral use may be in the form of hard gelatine capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin. They may also be in the form of soft gelatine capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions normally contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspension. Such expicients may be (1) suspending agent such as sodium carboxymethyl cellulose, methyl cellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; (2) dispersing or wetting agents which may be (a) naturally occurring phosphatide such as lecithin; (b) a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate; (c) a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadecaethylenoxycetanol; (d) a condensation product of ethylene oxide with a partial ester derived from a fatty acid and hexitol such as polyoxyethylene sorbitol monooleate, or (e) a condensation product of ethylene oxide with a partial ester derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleagenous suspension. This suspension may be formulated according to known methods using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The Compounds of the invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperature but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

The compounds of the present invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidyl-cholines.

For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of Formula 1 are employed.

Dosage levels of the compounds of the present invention are of the order of about 0.5 mg to about 100 mg per kilogram body weight, with a preferred dosage range between about 20 mg to about 50 mg per kilogram body weight per day (from about 25 mg to about 5 g's per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage will vary depending upon the host treated and the particular mode of administration. For example, a formulation intended for oral administration to humans may contain 5 mg to 1 g of an active compound with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95 percent of the total composition. Dosage unit forms will generally contain between from about 5 mg to about 500 mg of active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, gender, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular disease undergoing therapy. The dosage needs to be individualized by the clinician.

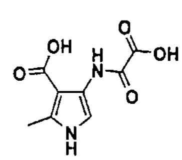
EXAMPLES

The process for preparing compounds of Formula 1 and preparations containing them is further illustrated in the following examples, which, however, are not to be construed as limiting.

Hereinafter, TLC is thin layer chromatography, $CDCl_3$ is deuterio chloroform and DMSO-d_6 is hexadeuterio dimethylsulfoxide. The structures of the compounds are confirmed by either elemental analysis or NMR, where peaks assigned to characteristic protons in the title compounds are presented where appropriate. ^1H NMR shifts (δ_H) are given in parts per million (ppm) downfield from tetramethylsilane as internal reference standard. M.p.: is melting point and is given in °C and is not corrected. Column chromatography was carried out using the technique described by W.C. Still *et al., J. Org. Chem. 43:* 2923 (1978) on Merck silica gel 60 (Art. 9385). HPLC analyses are performed using 5μm C18 4 x 250 mm column eluted with various mixtures of water and acetonitrile, flow = 1 ml/min, as described in the experimental section. Wang-resin is polystyrene with a 4-hydroxymethylphenol ether linker.
Compounds used as starting material are either known compounds or compounds which can readily be prepared by methods known per se.

2-Aminothiophenes are prepared according to Gewald *et al., Chem. Ber. 99:* 94 (1966).
3-Aminothiophenes are prepared according to H. Hartmann and J. Liebscher, Synthesis 275 (1984).

EXAMPLE 1



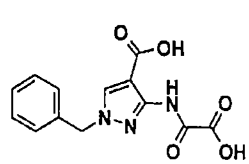
2-Methyl-4-(oxalyl-amino)-1H-pyrrole-3-carboxylic acid:

To a stirred solution of 4-(methoxyoxalyl-amino)-2-methyl-1H-pyrrole-3-carboxylic acid tert-butyl ester (2.0 g, 7.09 mmol) in dichloromethane (20 ml) was added trifluoro acetic acid (10 ml). The resulting reaction mixture was stirred at room temperature for 2 h. The volatiles were evaporated in vacuo affording 1.6 g (100 %) of 4-(methoxyoxalyl-amino)-2-methyl-1H-pyrrole-3-carboxylic acid as a solid.

To a solution of the above pyrrole-3-carboxylic acid (1.2 g, 5.31 mmol) in ethanol (100 ml) was added a solution of sodium hydroxide (0.47 g, 11.7 mmol) in water (50 ml). The resulting reaction mixture was stirred at room temperature for 18 h. The volatiles were evaporated in vacuo and the residue dissolved in water (100 ml). To the aqueous phase was added concentrated hydrochloric acid to pH = 1. The suspension was washed with ethyl acetate (50 ml) and dichloromethane (50 ml) and the precipitate was filtered off and dried in vacuo at 50 °C for 2 h. The solid was dissolved in isopropanol (100 ml), filtered and evaporated in vacuo affording 0.4 g (36%) of the title compound as a solid.

Calculated for $C_8H_8N_2O_5$, 0.1 x H_2O ;
C, 44.91 %; H, 3.86 %; N, 12.98 %. Found:
C, 45.06 %; H, 3.89 %; N, 12.72 %.

EXAMPLE 2



1-Benzyl-3-(oxalyl-amino)-1H-pyrazole-4-carboxylic acid:

To a stirred solution of 3-amino-1H-pyrazole-4-carboxylic acid ethyl ester (5.0 g, 0.032 mol) and triethylamine (9 ml) in dry tetrahydrofuran (150 ml) at 0 °C was added

dropwise ethyl oxalyl chloride (5.3 g, 0.039 mol). The resulting reaction mixture was stirred at room temperature for 18 h. An additional portion of ethyl oxalyl chloride (5.3 g, 0.039 mol) was added dropwise and the reaction mixture was stirred at room temperature for an additional 18 h. The volatiles were evaporated in vacuo and the residue dissolved in a mixture of water (200 ml) and ethyl acetate (200 ml). Undissolved matter was filtered off and dried in vacuo at 50 °C for 18 h affording 4.0 g (49 %) of 3-(ethoxyoxalyl-amino)-1H-pyrazole-4-carboxylic acid ethyl ester as a solid. The organic phase separated and washed with saturated aqueous sodium chloride (100 ml), dried ($MgSO_4$), filtered and the solvent evaporated in vacuo affording 3.7 g (45%) of 3-(ethoxyoxalyl-amino)-1H-pyrazole-4-carboxylic acid ethyl ester as a solid. A total yield of 7.7 g (94 %) was obtained.

To a solution of the above pyrazole-4-carboxylic acid ethyl ester (3.7 g, 0.015 mol) in dry N,N-dimethylformamide (75 ml) was added sodium hydride (640 mg, 0.016 mol, 60 % in mineral oil). The resulting reaction mixture was stirred at room temperature for 0.5 h. To the reaction mixture was added benzyl bromide (2.7 g, 0.016 mol) and the mixture was stirred at 50 °C for 4 h. Water (100 ml) was added and the reaction mixture was extracted with diethyl ether (2 x 100 ml). The combined organic extracts were washed with water (100 ml) saturated aqueous sodium chloride (2 x 50 ml), dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue (3.8 g) was purified on silicagel (800 ml) using a mixture of ethyl acetate and heptane (1:1) as eluent. Pure fractions were collected and the solvent evaporated in vacuo affording 0.9 g (18%) of 1-benzoyl-3-(ethoxyoxalyl-amino)-1H-pyrazole-4-carboxylic acid ethyl ester as a solid.

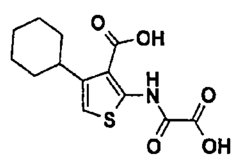
Unpure fraction were collected and the solvent evaporated in vacuo. The residue (1.0 g) was crystallised from diethyl ether (30 ml), filtered off and dried in vacuo at 50 °C for 2 h affording 0.9 g (18 %) of 1-benzoyl-3-(ethoxyoxalyl-amino)-1H-pyrazole-4-carboxylic acid ethyl ester as a solid. A total yield of 1.8 g (36 %) were collected.

To a solution of the above 1H-pyrazole-4-carboxylic acid ethyl ester (0.9 g, 2.61 mmol) in ethanol (50 ml) was added a solution of sodium hydroxide (0.26 g, 6.51 mmol) in water (25 ml). The resulting reaction mixture was stirred at room temperature for 60 h. The volatiles were evaporated in vacuo and the residue dissolved in

water (100 ml). To the aqueous phase was added concentrated hydrochloric acid to pH = 1. The precipitate was filtered off and dried in vacuo at 50 °C for 18 h. affording 0.55 g (73%) of the title compound as a solid.

M.p.: 189 - 191 °C:
Calculated for $C_{13}H_{11}N_3O_5$, 1.75 x H_2O;
C, 48.68 %; H, 4.56 %; N, 13.10 %. Found:
C, 48.81 %; H, 4.17 %; N, 12.84 %.

EXAMPLE 3

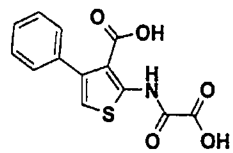


4-Cyclohexyl-2-(oxalyl-amino)-thiophene-3-carboxylic acid:

To a solution of 4-cyclohexyl-2-(ethoxyoxalyl-amino)-thiophene-3-carboxylic acid (60 mg, 0.18 mmol) in ethanol (10 ml) was added a solution of 1N sodium hydroxide (0.5 ml) in water (5 ml). The resulting reaction mixture was stirred at room temperature for 18 h. To the reaction mixture was added concentrated hydrochloric acid to pH = 1. The precipitate was filtered off and dried in vacuo at 50 °C for 18 h. affording 30 mg (55 %) of the title compound as a solid.

M.p.: > 250 °C:
Calculated for $C_{13}H_{15}NO_5S$, 1.5 x H_2O;
C, 48.14 %; H, 5.59 %; N, 4.32 %. Found:
C, 47.84 %; H, 9.92 %; N, 4.21 %.

EXAMPLE 4



2-(Oxalyl-amino)-4-phenyl-thiophene-3-carboxylic acid:

To a solution of 4-phenyl-2-(ethoxyoxalyl-amino)-thiophene-3-carboxylic acid ethyl ester (2.2 g, 6.33 mmol) in ethanol (50 ml) was added sodium hydroxide (630 mg, 15.83 mmol) in water (25 ml). The resulting reaction mixture was stirred at room temperature for 18 h., the volatiles were evaporated in vacuo and the residue was dissolved in water (100 ml) and washed with diethyl ether (2 x 100 ml). To the aqueous phase was added concentrated hydrochloric acid to pH = 1 and the resulting mixture was extracted with diethyl ether (2 x 100 ml). The combined organic phases were washed with saturated aqueous sodium chloride (100 ml), dried ($MgSO_4$), filtered and evaporated in vacuo affording 0.8 g of a mixture of mono ethyl ester and title compound according to NMR. The product mixture was dissolved in a mixture of ethanol (40 ml), water (20 ml) and sodium hydroxide (400 mg) and the resulting mixture was stirred at room temperature for 18 h., the volatiles were evaporated in vacuo and the residue was dissolved in water (50 ml) and washed with diethyl ether (50 ml). To the aqueous phase was added concentrated hydrochloric acid to pH = 1 and the precipitate was filtered off, washed with diethyl ether and dissolved in 2-propanol (25 ml). Undissolved matter was filtered off and the organic phase evaporated in vacuo affording 180 mg (10 %) of the title compound as a solid.

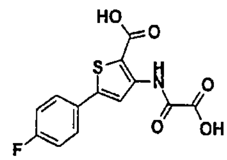
M.p.: 196 - 198 °C:

Calculated for $C_{13}H_9NO_5S$, 0.5 H_2O;

C, 52.00 %; H, 3.36 %; N, 4.66 %. Found:

C, 52.21 %; H, 3.44 %; N, 4.50 %.

EXAMPLE 5



5-(4-Fluoro-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid:

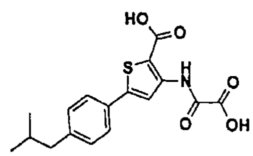
To an ice cooled solution of 5-(4-fluorophenyl)-3-aminothiophene-2-carboxylic acid methyl ester (1.0 g, 4.0 mmol) and triethylamine (11.1, 80 mmol) in dry tetrahydrofuran (40 ml) was added dropwise ethyl oxalyl chloride (1.2 g, 9.0 mmol). After stirring for 2 h, the reaction mixture was filtered and the solvent evaporated in vacuo. The residue was dissolved in dichloromethane, washed with 0.1 N HCl (2 x-dicared). The organic phase was dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was submitted to flash chromatography using toluene/ethyl acetate (19:1) as eluent, to give 1.19 g (85 %) of 5-(4-fluorophenyl)-3-(ethoxyoxalylamino)-thiophene-2-carboxylic acid ethyl ester.

To a solution of 5-(4-fluorophenyl)-3-(ethoxyoxalylamino)-thiophene-2-carboxylic acid ethyl ester (1.19 g, 3.4 mmol) in methanol (150 ml) was added 2 N sodium hydroxide (20 ml). The reaction mixture was stirred at 60 °C for 18 h. The volatiles were evaporated in vacuo. To the residue was added water and 1N hydrochloric acid to pH = 1., The aqueous phase was extracted with a mixture of dichloromethane/2-propanol. The organic phase was dried ($MgSO_4$), filtered and the solvent evaporated in vacuo. The residue was recrystallised from methanol/water to give 619 mg (67 %) of the title compound as a solid.

Calculated for $C_{13}H_8FNO_5S$, 0.5 H_2O;
C, 49.06 %; H, 2.83%; N, 4.40 %. Found:
C, 49.06 %; H, 2.72%; N, 4.31%.

In a similar way as described in Example 5 the following compounds were prepared.

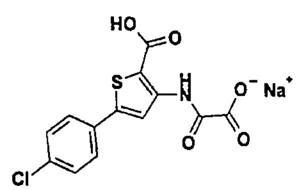
EXAMPLE 6



5-(4-Isobutyl-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

Calculated for $C_{17}H_{17}NO_5S$, 0.33 x H_2O;
C, 57.79 %; H, 5.00 %; N, 3.96 %. Found:
C, 57.79 %; H, 5.08 %; N, 3.89 %.

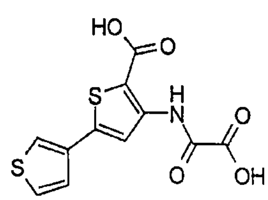
EXAMPLE 7



5-(4-Chloro-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid, mono sodium salt;

M.p.: > 250 °C:
Calculated for $C_{13}H_7ClNO_5SNa$, 1x H_2O;
C, 42.63 %; H, 2.52 %; N, 3.55 %. Found:
C, 42.69 %; H, 2.48 %; N, 3.83 %.

EXAMPLE 8



4-(Oxalyl-amino)-[2,3]-bithiophenyl-5-carboxylic acid;

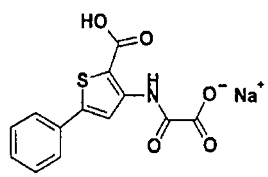
M.p.: 220 - 222 °C:

Calculated for $C_{11}H_7NO_5S_2$;

C, 44.44 %; H, 2.37 %; N, 4.71 %. Found:

C, 44.17 %; H, 2.43 %; N, 4.54 %.

EXAMPLE 9



3-(Oxalyl-amino)-5-phenyl-thiophene-2-carboxylic acid, mono sodium salt;

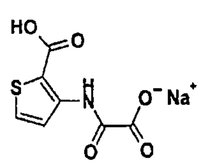
M.p.: > 250 °C:

Calculated for $C_{13}H_8NO_5SNa$, 1.6 x H_2O;

C, 45.64 %; H, 3.30 %; N, 4.09 %. Found:

C, 45.25 %; H, 2.93 %; N, 3.92 %.

EXAMPLE 10



3-(Oxalyl-amino)-thiophene-2-carboxylic acid, mono sodium salt;

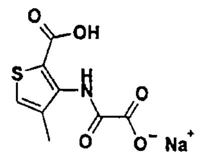
M.p.: > 250 °C:

Calculated for $C_7H_7NO_5SNa$, 1.5 x H_2O;

C, 31.83 %; H, 2.67 %; N, 5.30 %. Found:

C, 32.23 %; H, 3.14 %; N, 5.15 %.

EXAMPLE 11



4-Methyl-3-(oxalyl-amino)-thiophene-2-carboxylic acid, mono sodium salt;

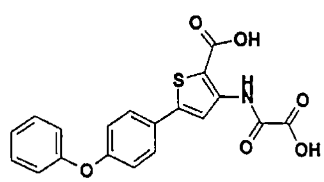
M.p.: 232 - 234 °C:

Calculated for $C_8H_6NO_5SNa$, 1.5 x H_2O;

C, 34.54 %; H, 3.26 %; N, 5.03 %. Found:

C, 34.58 %; H, 3.30 %; N, 4.81 %.

EXAMPLE 12



3-(Oxalyl-amino)-5-(4-phenoxy-phenyl)-thiophene-2-carboxylic acid

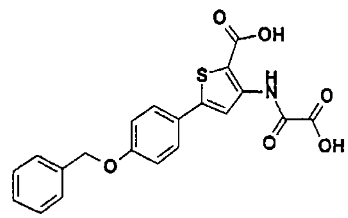
M.p.: 230 °C (decomp.)

Calculated for $C_{19}H_{13}NO_6S$, 1.25 x H_2O

C, 56.22 %; H, 3.85 %; N, 3.45 %. Found:

C, 56.00 %; H, 3.57 %; N, 3.39 %.

EXAMPLE 13



5-(4-Benzyloxy-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid

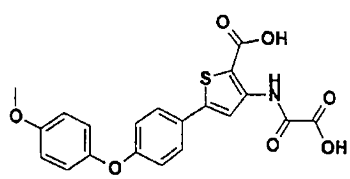
M.p.: 210 °C (decomp.)

Calculated for $C_{20}H_{15}NO_6S$

C, 60.45 %; H, 3.80 %; N, 3.52 %. Found:

C, 59.94 %; H, 3.79 %; N, 4.45 %.

EXAMPLE 14



5-(4-(4-Methoxy-phenoxy)-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid

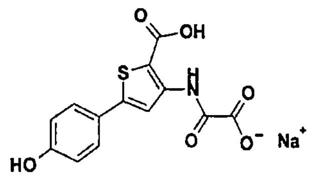
M.p.: 215 °C (decomp.)

Calculated for $C_{20}H_{15}NO_7S$, 1.5 H_2O

C, 54.54 %; H, 4.12 %; N, 3.18 %. Found:

C, 54.80 %; H, 3.88 %; N, 3.15 %.

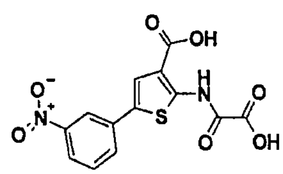
EXAMPLE 15



5-(4-Hydroxy-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid, mono sodium salt

M.p.: 205 - 206 °C
Calculated for $C_{13}H_9NO_6SNa_1$, 0.75 x H_20
C, 45.42 %; H, 3.08 %; N, 4.07 %. Found:
C, 45.11 %; H, 3.16 %; N, 3.98 %.

EXAMPLE 16



5-(3-Nitro-phenyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid:

To 3-nitrophenethyl alcohol (102 mg, 0.61 mmol) in dichloromethane (2.2 ml) at room temperature under nitrogen was added a solution of Dess-Martin periodinane reagent (285 mg, 0.67 mmol) in dichloromethane (2.7 ml). The reaction was stirred at room temperature under nitrogen for 45 minutes, at which time TLC analysis (hexane/ethyl acetate, 50/50) indicated the reaction was complete. Diethyl ether (5.0 ml) was added followed by a solution of 10 % sodium sulfite/saturated sodium bicarbonate (5.0 ml, 1:1). The emulsion gradually turned to a clear heterogeneous solution after standing for 10 minutes. Additional dichloromethane was added and the organic phase was washed with water (5 ml), dried ($MgSO_4$), filtered and evaporated in vacuo which afforded 100 mg (100 %) of 3-nitrophenyl-acetaldehyde as a clear oil. The aldehyde was used without further purification in the next step.

^1H NMR (400 MHz, $CDCl_3$) δ 3.90 (s, 2H), 7.65 (d, 2H), 8.20 (s, 1H), 8.25 (m, 1H), 9.90 (s, 1H).

A mixture of *tert*-butyl cyanoacetate (67 mg, 0.48 mmol), 3-nitrophenyl acetaldehyde (86 mg, 0.52 mmol), triethylamine (73 µl, 0.52 mmol) and elemental sulfur (17 mg, 0.52 mmol) in N,N-dimethylformamide (0.5 ml) was stirred at 60 °C for 1.5 h. After cooling to room temperature, the dark solution was diluted with ethyl acetate and washed with water (3 x 5 ml). The organic layer was dried ($MgSO_4$), filtered and the solvent evaporated in vacuo which afforded crude 2-amino-5-(3-nitro-phenyl)-thiophene-3-carboxylic acid *tert*-butyl ester (191 mg). Purification by preparative TLC (hexane/ethyl acetate, 80/20) afforded 74 mg (49 %) of 2-amino-5-(3-nitro-phenyl)-thiophene-3-carboxylic acid *tert*-butyl ester as a solid.

^1H NMR (400 MHz, $CDCl_3$) δ 1.56 (s, 9H), 6.05 (s, 2H), 7.20 (s, 1H), 7.40 (t, 1H), 7.68 (d, 1H), 7.90 (d, 1H), 8.25 (s, 1H).

A solution of 2-amino-5-(3-nitro-phenyl)-thiophene-3-carboxylic acid *tert*-butyl ester (66 mg, 0.21 mmol), imidazol-1-yl-oxoacetic acid *tert*-butyl ester (202 mg, 1.03 mmol) and triethylamine (40.4 µl, 0.21 mmol) in tetrahydrofuran (0.5 ml) was stirred at room temperature for 3 h. The volatiles were evaporated in vacuo and the residue was dissolved in ethyl acetate and washed successively with water (3 x 5 ml) and brine (5 ml). The organic layer was dried (Na_2SO_4), filtered and the solvent evaporated in vacuo affording crude product. Purification by preparative TLC gave 91 mg (98 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(3-nitrophenyl)-thiophene-3-carboxylic acid *tert*-butyl ester as a solid.

^1H NMR (400 MHz, $CDCl_3$) δ 1.54 (s, 9H), 1.62 (s, 9H), 7.5 (s, 1H), 7.55 (t, 1H, J = 8.4 Hz), 7.84 (d, 2H, J = 8.4 Hz), 8.16 (d, 1H, J = 8.4 Hz), 8.45 (s, 1H).

MS *m/z*: 447 (M-1).

The above 3-nitrophenyl-thiophene (85 mg, 0.19 mmol) was dissolved in a 20 % solution of trifluoroacetic acid in dichloromethane (3.0 ml) and stirred at room tempe-

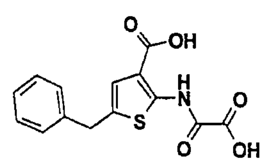
rature for 6 h. The solution was co-evaporated in vacuo with toluene affording 64 mg (100 %) of the title compound.

^{1}H-NMR (400 MHz, CD_3OD) δ 7.71 (t, 1H, J = 8.25 Hz), 7.8 (s, 1H), 8.1 (d, 1H, J = 7.5 Hz), 8.2 (d, 1H, J = 9 Hz), 7.86 (m, 1H).

MS *m/z*: 335 (M-1).

The following examples were prepared in a similar way as described in Example 16.

EXAMPLE 17



2-(Oxalyl-amino)-5-(phenyl-methyl)thiophene-3-carboxylic acid

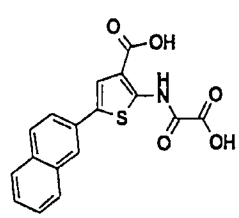
M.p.: 230 - 231 °C

Calculated for $C_{14}H_{11}NO_5S$.

C, 54.89 %; H, 3.63 %; N, 4.40 %. Found:

C, 54.94 %; H, 3.63 %; N, 4.43 %.

EXAMPLE 18

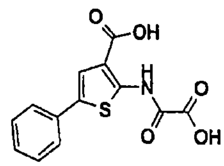


5-(Naphthalen-2-yl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid:

^{1}H NMR (400 MHz, CD_3OD) δ 7.42 - 7.49 (m, 2H), 7.66 (d, 1H, J = 4.5 Hz), 7.75 (m, 1H), 7.8 - 7.9 (m, 3H), 8.04 (d, 1H ,J = 7.5 Hz).

MS *m/z*: 340 (M-1).

EXAMPLE 19



2-(Oxalyl-amino)-5-phenyl-thiophene-3-carboxylic acid;

M.p.: 238 - 240 °C

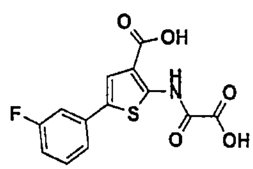
^{1}H NMR (400 MHz, CD_3OD) δ 7.3 (t, 1H, J = 4.5 Hz), 7.38 (t, 1H, J = 4.5Hz), 7.54 (s, 1H), 7.61 (m, 3H).

Calculated for $C_{13}H_9NO_5S$, 1 x H_2O;

C, 47.13 %; H, 3.04 %; N, 4.23 %. Found:

C, 47.34 %; H, 3.53 %; N, 4.20 %.

EXAMPLE 20

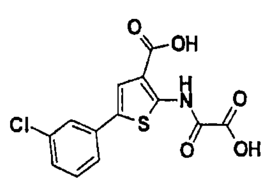


5-(2-Fluoro-phenyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

^{1}H NMR (400 MHz, CD_3OD) δ 7.18 - 7.23 (m, 2H), 7.30 (m, 1H), 7.63 -7.69 (m, 2H).

MS *m/z*: 308 (M-1).

EXAMPLE 21

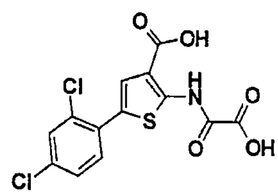


5-(3-Chloro-phenyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

Yield: 99 %.
^{1}H NMR (400 MHz, CD_3OD) δ 7.28 (m, 1H), 7.38 (m, 1H), 7.52 - 7.61 (m, 3H).

MS *m/z*: 324 (M-1).

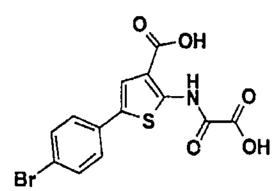
EXAMPLE 22



5-(2,4-Dichloro-phenyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

^{1}H NMR (400 MHz, CD_3OD) δ 7.37 (m, 1H), 7.39 (m, 1H), 7.52-7.58 (m, 3H).
MS *m/z*: 358 (M-1).

EXAMPLE 23

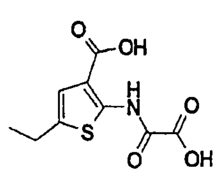


5-(4-Bromo-phenyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

^{1}H NMR (400 MHz, CD_3OD) δ 7.51 (s, 4H), 7.54 (s, 1H).

MS *m/z*: 370 (M-1).

EXAMPLE 24

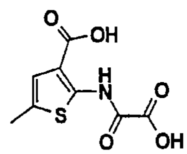


5-Ethyl-2-(oxalyl-amino)-thiophene-3-carboxylic acid:

^{1}H NMR (400 MHz, CD_3OD) δ 1.35 (t, 3H, J = 3.75), 2.95 (q, 2H), 7.05 (s, 1H).

MS *m/z*: 170.2 (M-73) (-COCOOH), 228.1 (M-1).

EXAMPLE 25

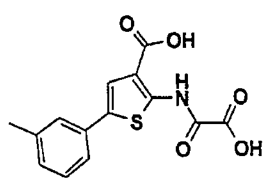


5-Methyl-2-(oxalyl-amino)-thiophene-3-carboxylic acid:

^{1}H NMR (400 MHz, CD_3OD) δ 2.6 (s, 3H), 7.05 (s, 1H).

MS *m/z*: 228 (M-1).

EXAMPLE 26

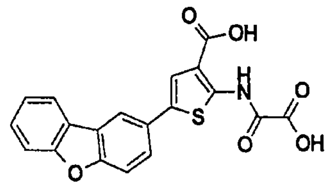


5-(3-Methyl-phenyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid:

^{1}H NMR (400 MHz, CD_3OD) δ 2.39 (s, 3H), 7.12 (d, 1H, J = 8 Hz), 7.25 (t, 1H, J = 7.5 Hz), 7.4 (m, 2H), 7.5 (s, 1H).

MS *m/z* 304, 232 (M-1).

EXAMPLE 27

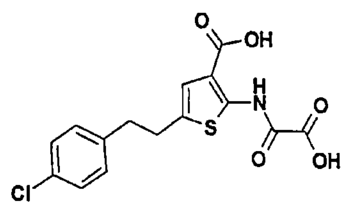


5-Dibenzofuran-2-yl-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

^{1}H NMR (400 MHz, CD_3COCD_3) δ 7.4 (t, 1H , J = 2 Hz), 7.52 (t, 1H, J = 2 Hz), 7.7 (m, 3H), 7.9 (t, 1H, J = 2 Hz), 8.25 (d, 1H, J = 2 Hz), 8.5 (s, 1H).

MS *m/z* 380.5 (M-1).

EXAMPLE 28



5-(2-(4-Chloro-phenyl)-ethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid, mono sodium salt

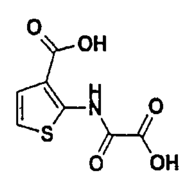
M.p.: > 250 °C

Calculated for $C_{15}H_{11}N_1Cl_1O_5S_1Na_1$, 0.75 x H_20

C, 46.28 %; H, 3.24 %; N, 3.60 %. Found:

C, 46.17 %; H, 3.38 %; N, 3.40 %.

EXAMPLE 29



2-(Oxalyl-amino)-thiophene-3-carboxylic acid;

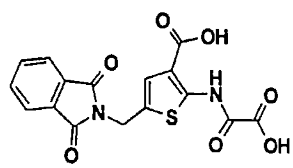
M.p.: 225 - 228 °C

Calculated for $C_7H_5N_1O_5S_1$, 1.25 x H_20

C, 35.37 %; H, 3.18 %; N, 5.89 %. Found:

C, 35.53 %; H, 2.82 %; N, 5.72 %.

EXAMPLE 30



5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)thiophene-3-carboxylic acid:

To a stirred mixture at 0 °C of 2-(3-hydroxy-propyl)-isoindole-1,3-dione (0.2 g, 0.97 mmol), 0.7 M sodium bromide (0.70 ml, 0.46 mmol), TEMPO (3.0 mg, 0.02 mmol) in dichloromethane (1 ml) was added dropwise a solution of bleach (2.1 ml, 4.9 mmol) and sodium hydrogen carbonate (117 mg, 1.4 mmol). The mixture was stirred at 0 °C for 2 hours after the addition was finished. The mixture was extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were washed with 10% sodium thiosulphate (3 x 10 ml), brine (10 ml), dried ($MgSO_4$), filtered and the solvent was evaporated in vacuo. The residue was washed with ethyl acetate (2 x 1 ml) affording after drying 161 mg (81 %) of 3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionaldehyde as a solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.82 (s, 1H), 7.85 (dd, 2H, J = 5.6, 2.8 Hz), 7.73 (dd, 2H, J = 5.6, 2.8 Hz), 4.04 (t, 2H, J = 7.2 Hz), 2.89 (t, 2H, J = 7.2 Hz).

To a solution of the above aldehyde (150 mg, 0.74 mmol), triethylamine (113 ml, 0.81 mmol) and sulfur (24 mg, 0.81 mmol) in dichloromethane (10 ml) at room temperature was added *tert*-butyl cyanoacetate (114 mg, 0.81 mmol). The mixture was stirred and heated at reflux temperature under nitrogen for 2 h. After cooled to room

temperature the precipitate was filtered off affording 189 mg of 2-amino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-thiophene-3-carboxylic acid *tert*-butyl ester as a solid.

The filtrate was evaporated in vacuo, the residue was taken into ethyl acetate (50 ml), washed with 0.5 N hydrochloric acid (2 x 10 ml), saturated sodium bicarbonate (2 x 10 ml), brine (10 ml), dried ($MgSO_4$) and filtered. The solvent was evaporated in vacuo and the residue was washed with cold ethyl acetate (2 x 1 ml) affording 52 mg of 2-amino-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-thiophene-3-carboxylic acid *tert*-butyl ester as a solid. A total yield of 241 mg (91 %) was obtained.

^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, 2H, J = 7.2, 4 Hz), 7.72 (dd, 2H, J = 7.2, 4 Hz), 6.97 (s, 1H), 5.83 (s, 2H, NH_2), 4.78 (s, 2H), 1.56 (s, 9H)

To a stirred solution of the above thiophene (100 mg, 0.28 mmol) in tetrahydrofuran (2 ml) was added a solution of imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (60 mg, 0.31 mmol) in tetrahydrofuran (1 ml). The mixture was stirred at room temperature for 3 h. The solvent was evaporated in vacuo. The residue was dissolved in ethyl acetate (50 ml), washed with 0.5 N hydrochloric acid (2 x 5 ml), saturated sodium bicarbonate (2 x 5 ml), brine (5 ml), dried ($MgSO_4$) and filtered. The solvent was evaporated in vacuo affording 130 mg (96 %) of 2-(*tert*-butoxyoxalyl-amino)-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-thiophene-3-carboxylic acid *tert*-butyl ester as a solid.

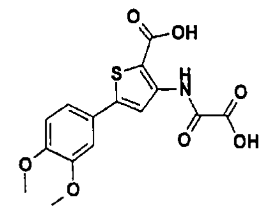
^1H NMR (400 MHz, $CDCl_3$) δ 12.23 (s, 1H), 7.87 (dd, 2H, J = 7.2, 4 Hz), 7.73 (dd, 2H, J = 7.2, 4 Hz), 7.24 (s, 1H), 4.93 (s, 2H), 1.60 (s, 9H), 1.57 (s, 9H).

To a solution of trifluoroacetic acid (1 ml) in dichloromethane (1 ml) was added the above ditert-butyl ester (100 mg, 0.21 mmol). The solution was stirred at room temperature for 1 h. The solvent was evaporated in vacuo. The residue was washed with dichloromethane (3 x 1 ml) which afforded 63 mg (82 %) of the title compound as a solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.05 (s, 1H), 7.89 (m, 2H), 7.87 (m, 2H), 7.10 (s, 1H), 4.83 (s, 2H).

MS *m/z*: 373 (M-1).

EXAMPLE 31



5-(3,4-Dimethoxy-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid

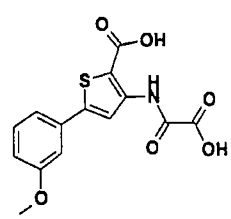
M.p.: 230 - 231 °C

Calculated for $C_{15}H_{13}N_1O_7S_1$, 1 x H_20

C, 48.78 %; H, 4.09 %; N, 3.79 %. Found:

C, 49.01 %; H, 3.75 %; N, 3.79 %.

EXAMPLE 32



5-(3-Methoxy-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid

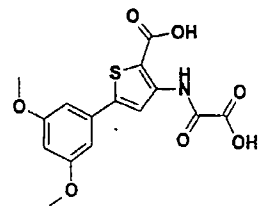
M.p.: 217 - 218 °C

Calculated for $C_{14}H_{11}N_1O_6S_1$, 0.75 x H_20

C, 50.22 %; H, 3.76 %; N, 4.18 %. Found:

C, 50.02 %; H, 3.73 %; N, 4.16 %.

EXAMPLE 33



5-(3,5-Dimethoxy-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid

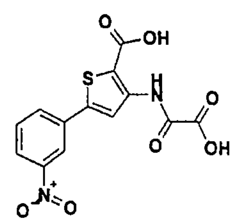
M.p.: 223 - 225 °C

Calculated for $C_{15}H_{13}N_1O_7S_1$, 1.25 x H_20

C, 48.19 %; H, 4.18 %; N, 3.75 %. Found:

C, 48.25 %; H, 4.10 %; N, 3.39 %.

EXAMPLE 34



5-(3-Nitro-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid

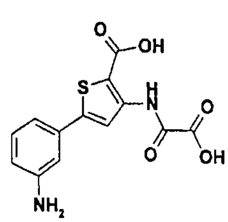
M.p.: > 250 °C

Calculated for $C_{13}H_7N_1O_7S_1Na_1$, 1.25 x H_20

C, 41.01 %; H, 2.51 %; N, 7.36 %. Found:

C, 41.03 %; H, 2.38 %; N, 7.17 %.

EXAMPLE 35



5-(3-Amino-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid

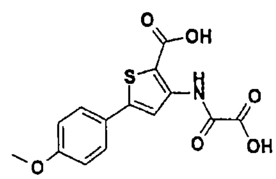
M.p.: > 250 °C

Calculated for $C_{13}H_{10}N_2O_5S_1$, 0.5 x H_20

C, 49.52 %; H, 3.52 %; N, 8.88 %. Found:

C, 49.48 %; H, 3.44 %; N, 8.71 %.

EXAMPLE 36



5-(4-Methoxy-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid

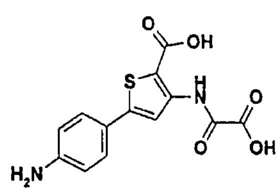
M.p.: 220 - 221 °C

Calculated for $C_{14}H_{11}N_1O_6S_1$, 0.4 x H_20

C, 51.19 %; H, 3.62 %; N, 4.62 %. Found:

C, 51.29 %; H, 3.53 %; N, 3.96 %.

EXAMPLE 37



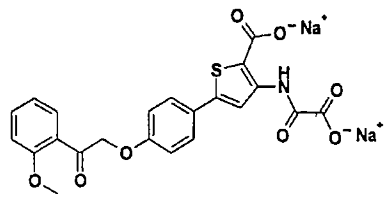
5-(4-Amino-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid:

Calculated for $C_{13}H_{10}N_2O_5S_1$, 0.5 x H_20

C, 49.52 %; H, 3.52 %; N, 8.88 %. Found:

C, 49.40 %; H, 3.87 %; N, 8.23 %.

EXAMPLE 38



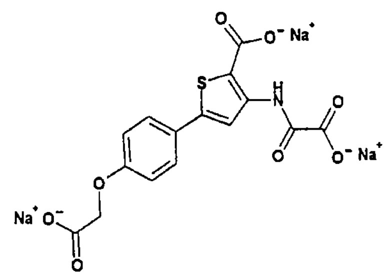
5-(4-(2-(2-Methoxy-phenyl)-2-oxo-ethoxy)-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid, disodium salt

To a solution of 3-(ethoxyoxalylamino)-5-(4-hydroxyphenyl)thiophene-2-carboxylic acid methyl ester (524 mg, 1.5 mmol) and potassium carbonate (275 mg, 2.0 mmol) in N,N-dimethylformamide (35 ml) was under an nitrogen atmosphere added ω-brom-2-methoxyacetophenon (460 mg, 2.0 mmol). After stirring for 3 h, the precipitate crude 3-(ethoxyoxalylamino)-5-(4-(2-(2-methoxyphenyl)-2-oxy-ethoxy)phenyl)-thiophene-2-carboxylic acid methyl ester (1.0 g) was filtered off.

To a solution of crude 3-(ethoxyoxalylamino)-5-(4-(2-(2-methoxyphenyl)-2-oxy-ethoxy)phenyl)-thiophene-2-carboxylic acid methyl ester (0.5 g) in methanol (15 ml) was added 1N sodium hydroxide (10 ml). After stirring at 65 °C for 3 h, the product was isolated by filtration and washed with a mixture of water and ethanol (1:1) affording after drying in vacuo 290 mg of the title compound as a solid.

M.p.: 286 - 287 °C.
Calculated for $C_{22}H_{18}N_1O_9S_1Na_2$;
C, 50.19 %; H, 3.42 %; N, 2.66 %. Found:
C, 51.18 %; H, 3.42 %; N, 2.58 %.

EXAMPLE 39



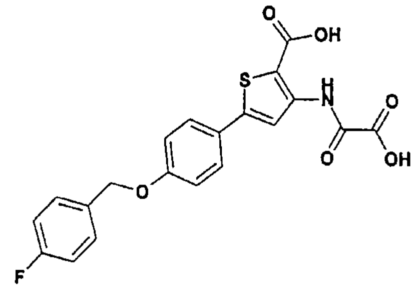
5-(4-Carboxymethoxy-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid, trisodium salt:

To a solution of 3-(ethoxyoxalylamino)-5-(4-hydroxyphenyl)thiophene-2-carboxylic acid methyl ester (307 mg, 1.0 mmol) and potassium carbonate (166 mg, 1.2 mmol) in N,N-dimethylformamide (5 ml) was added 2-bromoacetamide (165 mg, 1.2 mmol). After stirring at 50 °C for 16 h, the reaction mixture was quenched by addition of water, and the precipitate 5-(4-carbamoylmethoxy-phenyl)-3-(ethoxyoxalylamino)-thiophene-2-carboxylic acid methyl ester (70 mg) was isolated by filtration. The aqueous phase was acidified with 1N hydrochloric to pH = 1-2 and the semi hydrolysed product, 5-(4-carbamoylmethoxy-phenyl)-3-(oxalylamino)-thiophene-2-carboxylic acid methyl ester (300 mg), was isolated by filtration. To a suspension of 5-(4-carbamoylmethoxy-phenyl)-3-(oxalylamino)-thiophene-2-carboxylic acid methyl ester (295 mg, 0.78 mmol) in methanol (5 ml) and water (5 ml) was added 1 N sodium hydroxide (2 ml). After stirring for 5 days the precipitate was filtered off affording 105 mg (88 %) of the title compound as a solid.

M.p.: > 300 °C.
Calculated for $C_{15}H_{12}N_1O_{10}S_1Na_3$;
C, 38.56 %; H, 2.59 %; N, 3.00 %. Found:
C, 38.73 %; H, 2.74 %; N, 3.06 %.

In a similar way as described in Example 37 the following compound was prepared:

EXAMPLE 40

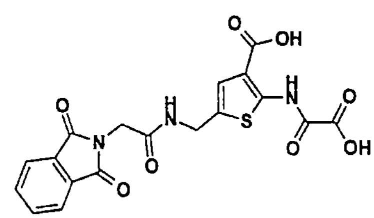


5-(4-(4-Fluoro-benzyloxy)-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid:

^{1}H NMR (300 MHz, DMSO d_6) δ 5.15 (s, 2H), 7.1 (d, 2H), 7.25 (t, 2H), 7.55 (q, 2H), 7.7 (d, 2H), 8.2 (s, 1H).

SP/MS: 415 (M+, 12%), 372, 353, 299, 218, 190, 162, 109 (100%).

EXAMPLE 41



5-((2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acetylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid:

To a solution of 2-(*tert*-butoxyoxalyl-amino)-5-(1,3-dioxo-1,3-dihydro-isoindol-2-ylmethyl)-thiophene-3-carboxylic acid *tert*-butyl ester (0.4 g, 0.82 mmol, prepared as described in example 30) in dichloromethane (2 ml) was added anhydrous hydrazine (28 ml, 0.9 mmol) and the mixture stirred at ambient temperature for 19 h under nitrogen. An additional portion of hydrazine (84 ml, 2.7 mmol) and dichloromethane (5.5 ml) was added and stirring was continued for an additional 88 h. Dichloromethane (50 ml) was added and the reaction mixture was placed in a sonicator for 20 min and filtered through Celite. The filtrate was evaporated in vacuo affording 0.24 g (82 %) of 5-aminomethyl-2-(*tert*-butoxyoxalyl-amino)-thiophene-3-carboxylic

acid *tert*-butyl ester as a solid which was used without further purification in the next step.

To a solution of (1,3-dioxo-1,3-dihydro-isoindol-2-yl)-acetic acid (0.17 g, 0.82 mmol), 1-hydroxybenzotriazole (0.133 g, 0.98 mmol) and 2,6 lutidine (0.4 ml) in dry acetonitrile (10 ml) under nitrogen cooled in an ice bath was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.21 g, 1.1 mmol) and the solution was stirred for 0.5 h. 5-Aminomethyl-2-(*tert*-butoxyoxalyl-amino)-thiophene-3-carboxylic acid *tert*-butyl ester (0.24 g, 0.68 mmol) was added, the cooling bath removed, and the solution stirred at ambient temperature for 20 h. The volatiles were evaporated in vacuo and the residue dissolved in dichloromethane and washed with saturated aqueous sodium bicarbonate and 1N hydrochloric acid, dried (Na_2SO_4) and the solvent evaporated in vacuo. The residue (0.18 g) was dissolved in dry tetrahydrofuran (6 ml) under nitrogen, imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (0.25 g, 1.3 mmol) was added and the solution stirred at ambient temperature for 17 h, the solvent evaporated in vacuo and the residue dissolved in a mixture of dichloromethane and saturated aqueous sodium bicarbonate solution. The organic layer was dried (Na_2SO_4) and the solvent evaporated in vacuo. The residue was subjected to chromatography on silica gel affording 0.1 g of 2-(*tert*-butoxyoxalyl-amino)-5-((2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-acetylamino)-methyl)-thiophene-3-carboxylic acid *tert*-butyl ester.

^{1}H NMR (400 MHz, $CDCl_3$) δ 12.3 (bs, 1H), 7.9 (m, 2H), 7.8 (m, 2H), 7.1 (s, 1H), 6.5 (m, 1H), 4.6 (m, 2H), 4.4 (s, 2H,), 1.8 (s, 9H), 1.6 (s, 9H).

To 2-(*tert*-butoxyoxalyl-amino)-5-((2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-acetylamino)-methyl)-thiophene-3-carboxylic acid *tert*-butyl ester (0.1 g, 0.18 mmol) was added 20 % trifluoroacetic acid in dichloromethane (4 ml) and the reaction mixture was stirred at ambient temperature under nitrogen for 14 h. The volatiles were evaporated in vacuo and the residue chased with dichloromethane until a solid remained. The precipitate was filtered off and dried in vacuo for 18 h affording in quantitative yield the title compound as a solid.

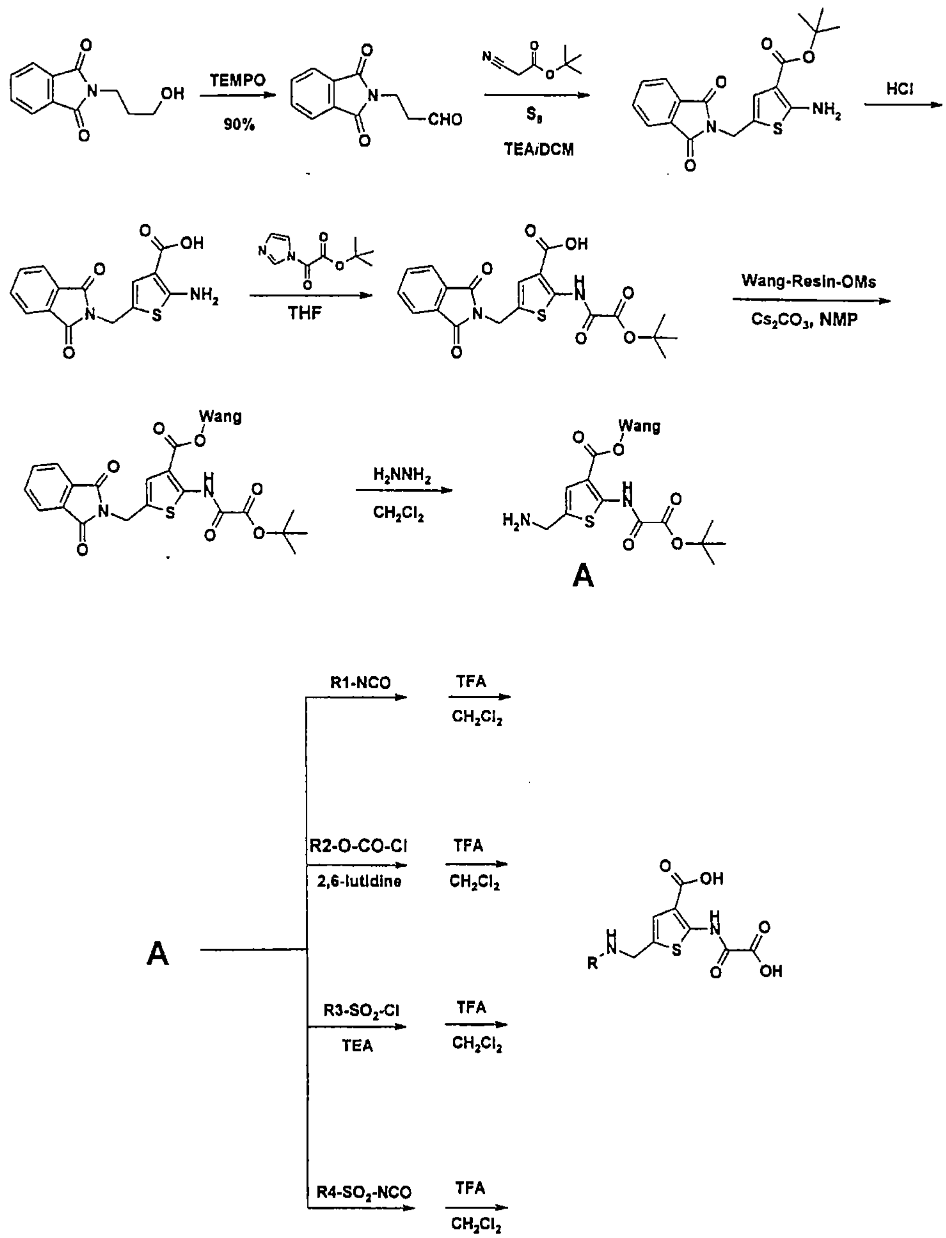
Mp. 243 – 244 °C (dec).

MS *m/z*: 430 (M-1).

^{1}H NMR (400 MHz, DMSO-d_6) δ 12.1 (s, 1H), 8.9 (s, 1H), 7.8 – 7.9 (m, 4H), 7.1 (s, 1H), 4.4 (m, 2H), 4.2 (s, 2H).

EXAMPLE 42

Using a solid phase chemistry approach a 64 member library was synthesised according to the following scheme



5-Aminomethyl-2-(*tert*-butoxyoxalyl-amino)-thiophene-3-carboxylic acid Wang- Resin ester (1.8 mmol) is weighed out and suspended in a mixture of tetrahydrofuran and dichloromethane (90 ml, 1:1). 1 ml of the suspension containing 20 μmol of the resin is dispensed to 64 wells (OntoBlock system). The wells are drained and dried under

vacuum for 2 h. Anhydrous N,N-dimethylformamide (1 ml) was dispensed to each well. The chemicals distributed to each well are listed as follow:

Ureas.

From well A1 through C8, 24 μmol of each isocyanate is dispensed into corresponding well.

Sulfonylureas.

From well D1 through D4, 40 μmol of each sulfonylisocyanate is dispensed into corresponding well.

Carbamates.

From well D5 through F7, 7.0 μL of 2,6-lutidine (60 μmol) is added to each of these wells followed by 40 μmol of corresponding sulfonylisocyanates.

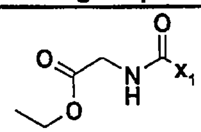
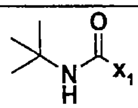
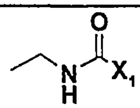
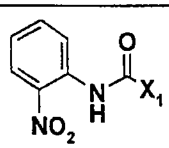
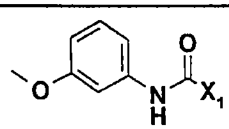
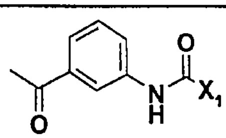
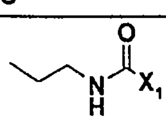
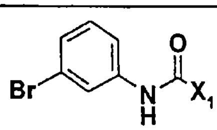
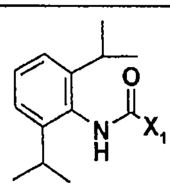
Sulfonamides.

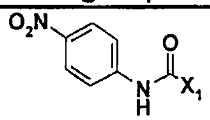
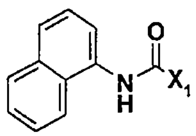
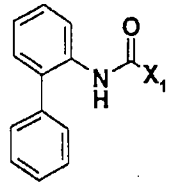
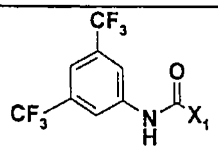
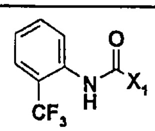
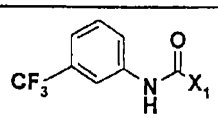
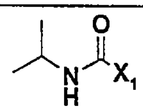
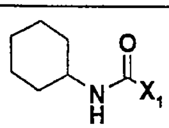
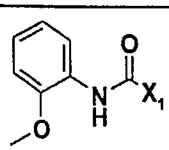
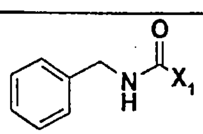
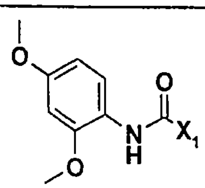
From well F8 through H8, 8.4 μL of triethylamine (60 μmol) is added to each of these wells followed by 40 μmol of corresponding sulfonylchlorides.

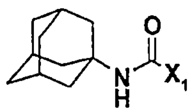
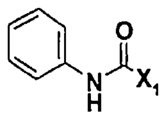
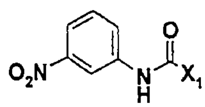
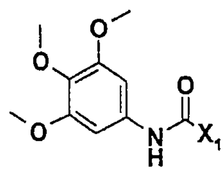
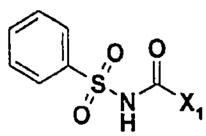
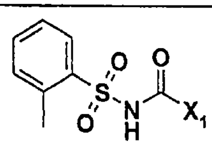
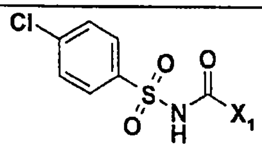
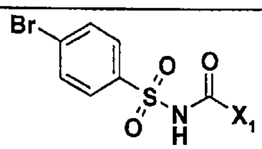
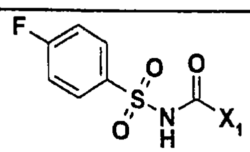
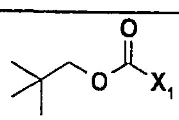
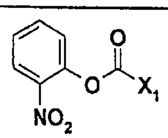
After distributing the chemicals (list of R-groups see below) to each well, the blocks are shaken at 500 rpm for 3 days and then drained, washed and dried under vacuum overnight. 1 ml solution of imidazol-1-yl-oxo-acetic acid *tert*-butyl ester (200 μmol) in dichloromethane is dispensed into each well under nitrogen. The blocks are shaken at 500 rpm overnight, drained, washed and dried under vacuum. 1 ml of trifluoroacetic acid/dichloromethane (1:1) was dispensed into each well of the blocks and drained into a microtitre plate 30 min after it is dispensed. Then 0.5 ml of trifluoroacetic acid/dichloromethane (1:1) was dispensed into each well of the blocks and drained to the microtiter plate 45 min after it is dispensed. The microtiter plate containing the products cleaved from the resin was dried in vacuo using a Gen-Vac to get the final products. The final products were analyzed by HPLC and MS.

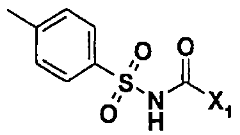
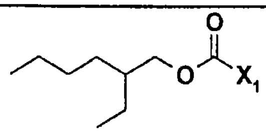
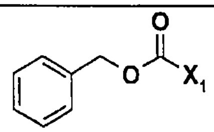
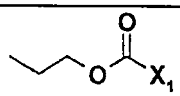
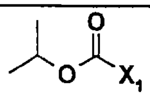
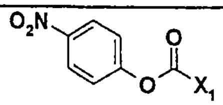
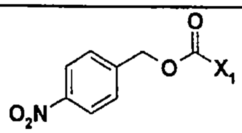
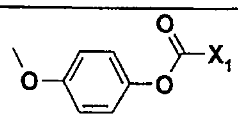
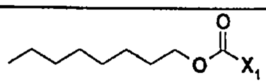
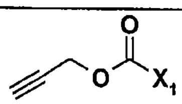
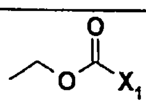
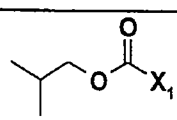
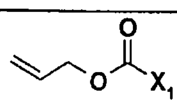
X_1 indicate point of attachment for the R-group.

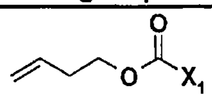
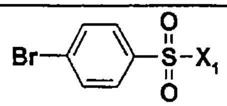
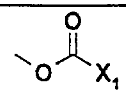
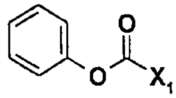
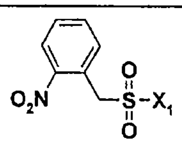
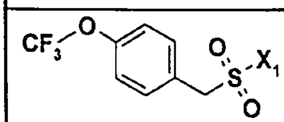
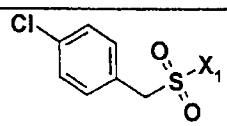
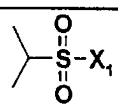
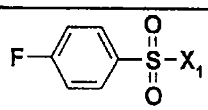
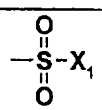
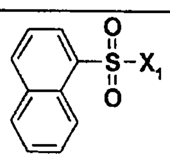
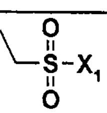
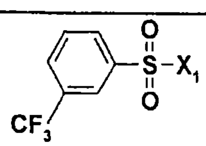
The percentage means the area of the peak of the HPLC at 220 nm.

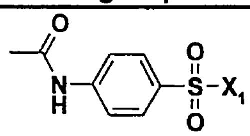
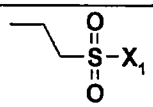
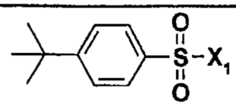
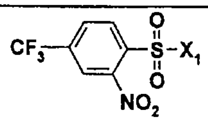
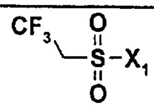
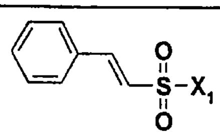
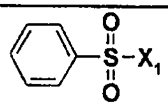
R-group	Formula	Mw	LC/MS
	C13H15N3O8S	373.34	No hit
	C13H17N3O6S	343.36	No hit
	C11H13N3O6S	315.31	No hit
	C15H12N4O8S	408.35	407 (M-H,44%)
	C16H15N3O7S	393.38	No hit
	C17H15N3O7S	405.39	No hit
	C12H15N3O6S	329.33	No hit
	C15H12BrN3O6S	442.25	442 (M-H, 50%)
	C21H25N3O6S	447.51	446 (M-H,92%)

R-group	Formula	Mw	LC/MS
	C15H12N4O8S	408.35	407 (M-H,48%)
	C19H15N3O6S	413.41	412 (M-H,49%)
	C21H17N3O6S	439.45	438 (M-H,81%)
	C17H11F6N3O6S	499.35	498 (M-H,83%)
	C16H12F3N3O6S	431.35	No hit
	C16H12F3N3O6S	431.35	430 (M-H,48%)
	C12H15N3O6S	329.33	328 (M-H,94%)
	C15H19N3O6S	369.40	368 (M-H,85%)
	C16H15N3O7S	393.38	No hit
	C16H15N3O6S	377.38	376 (M-H,86%)
	C17H17N3O8S	423.40	422 (M-H,39%)

R-group	Formula	Mw	LC/MS
	C19H23N3O6S	421.48	420 (M-H,29%)
	C15H13N3O6S	363.35	362 (M-H,26%)
	C15H12N4O8S	408.35	407 (M-H,44%)
	C18H19N3O9S	453.43	452 (M-H, 34%)
	C15H13N3O8S2	427.41	426 (M-H,62%)
	C16H15N3O8S2	441.44	440 (M-H,89%)
	C15H12ClN3O8S2	461.86	460 (M-H,41%)
	C15H11BrN2O7S	443.23	442 (M-H,71%)
	C15H11FN2O7S	382.33	381 (M-H,82%)
	C14H18N2O7S	358.37	357 (M-H,70%)
	C15H11N3O9S	409.33	408 (M-H,87%)

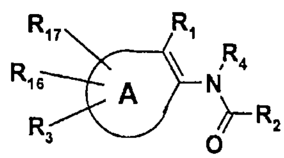
R-group	Formula	Mw	LC/MS
	C16H15N3O8S2	441.44	No Hit
	C17H24N2O7S	400.45	399 (M-H,68%)
	C16H14N2O7S	378.36	377 (M-H,63%)
	C12H14N2O7S	330.32	329 (M-H,54%)
	C12H14N2O7S	330.32	329 (M-H,76%)
	C15H11N3O9S	409.33	408 (M-H,82%)
	C16H13N3O9S	423.36	422 (M-H,63%)
	C16H14N2O8S	394.36	393 (M-H,78%)
	C17H24N2O7S	400.45	399 (M-H,78%)
	C12H10N2O7S	326.29	325 (M-H,92%)
	C11H12N2O7S	316.29	315 (M-H,70%)
	C13H16N2O7S	344.35	343 (M-H,86%)
	C12H12N2O7S	328.30	327 (M-H,73%)

R-group	Formula	Mw	LC/MS
	C13H14N2O7S	342.33	341 (M-H,74%)
	C14H11BrN2O7S2	463.28	362 (M-H,45%)
	C10H10N2O7S	302.26	301 (M-H,72%)
	C15H12N2O7S	364.34	363 (M-H,82%)
	C15H13N3O9S2	443.41	442 (M-H,94%)
	C15H11F3N2O8S2	468.39	467 (M-H,62%)
	C14H11ClN2O7S2	418.83	417 (M-H,31%)
	C11H14N2O7S2	350.37	349 (M-H,89%)
	C14H11FN2O7S2	402.38	401 (M-H,34%)
	C9H10N2O7S2	322.32	321 (M-H,50%)
	C18H14N2O7S2	434.45	433 (M-H,42%)
	C10H12N2O7S2	336.34	335 (M-H,46%)
	C15H11F3N2O7S2	452.39	451 (M-H,82%)

R-group	Formula	Mw	LC/MS
	C16H15N3O8S2	441.44	440 (M-H,42%)
	C11H14N2O7S2	350.37	349 (M-H,57%)
	C18H20N2O7S2	440.50	439(M-H,42%)
	C15H10F3N3O9S2	497.38	496 (M-H,68%)
	C10H9F3N2O7S2	390.32	389 (M-H,92%)
	C16H14N2O7S2	410.43	409 (M-H,46%)
	C14H12N2O7S2	384.39	383 (M-H,42%)

CLAIMS

1. A compound of Formula 1

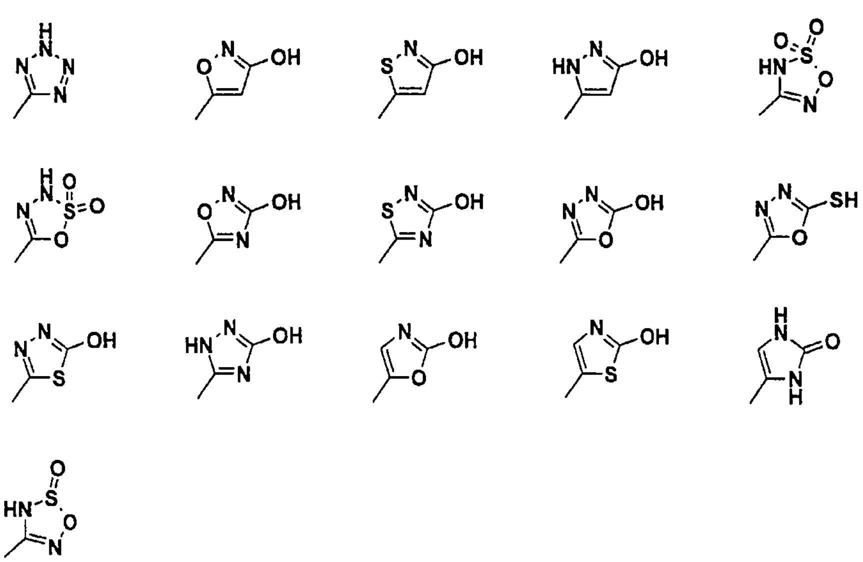


Formula 1

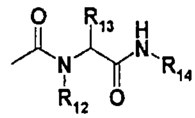
wherein

A is together with the double bond in Formula 1 furanyl, thiophenyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, furazanyl or 1,2,3-triazolyl;

R_1 is hydrogen, COR_5, OR_6, CF_3, nitro, cyano, CH_2OH, SO_3H, $SO_2NR_7R_8$, $PO(OH)_2$, $CH_2PO(OH)_2$, $CHFPO(OH)_2$, $CF_2PO(OH)_2$, $C(=NH)NH_2$, NR_7R_8 or selected from the following 5-membered heterocycles:

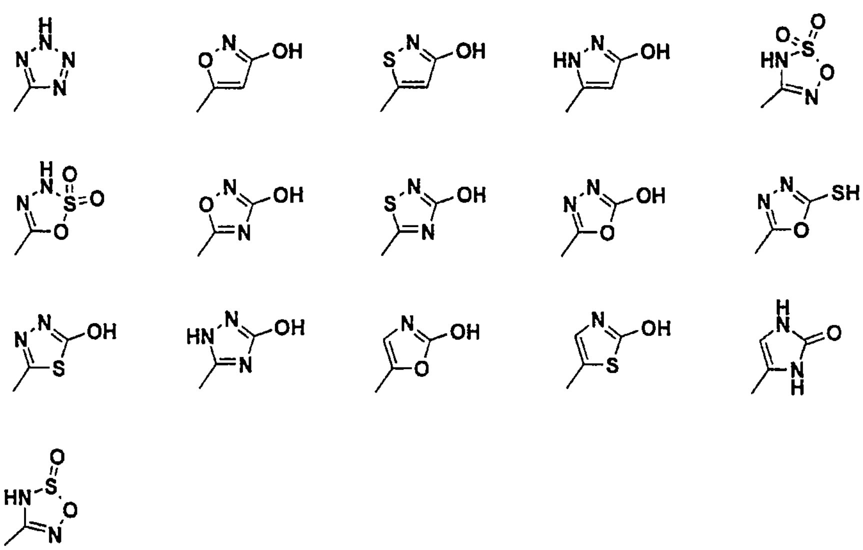


or R_1 is



wherein R_{12}, R_{13}, and R_{14} are independently hydrogen, C_1-C_6alkyl, aryl, arylC$_1$-C_6alkyl and the alkyl and aryl groups are optionally substituted;

R_2 is COR_5, OR_6, CF_3, nitro, cyano, SO_3H, $SO_2NR_7R_8$, $PO(OH)_2$, $CH_2PO(OH)_2$, $CHFPO(OH)_2$, $CF_2PO(OH)_2$, $C(=NH)NH_2$, NR_7R_8 , or selected from the following 5-membered heterocycles:



R_3, R_{16} and R_{17} are independently hydrogen, halo, nitro, cyano, trihalomethyl, C_1-C_6alkyl, aryl, arylC$_1$-C_6alkyl, hydroxy, oxo, carboxy, carboxyC$_1$-C_6alkyl, C_1-C_6alkyloxycarbonyl, aryloxycarbonyl, arylC$_1$-C_6alkyloxycarbonyl, C_1-C_6alkyloxy, C_1-C_6alkyloxyC$_1$-C_6alkyl, aryloxy, arylC$_1$-C_6alkyloxy, arylC$_1$-C_6alkyloxyC$_1$-C_6alkyl, thio, C_1-C_6alkylthio, C_1-C_6alkylthioC$_1$-C_6alkyl, arylthio, arylC$_1$-C_6alkylthio, arylC$_1$-C_6alkylthioC$_1$-C_6alkyl, NR_7R_8, C_1-C_6alkylaminoC$_1$-C_6alkyl, arylC$_1$-C_6alkylaminoC$_1$-C_6alkyl, di(arylC$_1$-

C_6alkyl)aminoC_1-C_6alkyl, C_1-C_6alkylcarbonyl, C_1-C_6alkylcarbonyl-C_1-C_6alkyl, arylC_1-C_6alkylcarbonyl, arylC_1-C_6alkylcarbonylC_1-C_6alkyl, C_1-C_6alkylcarboxy, C_1-C_6alkylcarboxyC_1-C_6-alkyl, arylcarboxy, arylcarboxyC_1-C_6alkyl, arylC_1-C_6alkylcarboxy, arylC_1-C_6alkylcarboxyC_1-C_6alkyl, C_1-C_6alkylcarbonylamino, C_1-C_6alkylcarbonylaminoC_1-C_6alkyl, -carbonylNR_7C_1-C_6alkylCOR_{11}, arylC_1-C_6alkylcarbonylamino, arylC_1-C_6alkylcarbonylaminoC_1-C_6alkyl, $CONR_7R_8$, or C_1-C_6alkyl$CONR_7R_8$ wherein the alkyl and aryl groups are optionally substituted and R_{11} is NR_7R_8; or C_1-C_6alkylNR_7R_8; or, when R_{16} and R_{17} are hydrogen, R_3 is

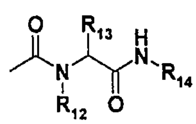
A-B-C-D-C_1-C_6alkyl, wherein

A is C_1-C_6alkyl, aryl or arylC_1-C_6alkyl;

B is amino, thio, SO, SO_2 or oxo;

C is C_1-C_6alkyl, amino;

D is a chemical bond, amino or C_1-C_6alkyl wherein the alkyl and aryl groups are optionally substituted; or



wherein R_{12}, R_{13}, and R_{14} are independently hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl and the alkyl and aryl groups are optionally substituted;

R_4 is hydrogen, hydroxy, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, NR_7R_8, C_1-C_6alkyloxy; wherein the alkyl and aryl groups are optionally substituted;

R_5 is hydroxy, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkyloxy, C_1-C_6alkyl-oxyC_1-C_6alkyloxy, aryloxy, arylC_1-C_6alkyloxy, CF_3, NR_7R_8; wherein the alkyl and aryl groups are optionally substituted;

R_6 is hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl; wherein the alkyl and aryl groups are optionally substituted;

R_7 and R_8 are independently selected from hydrogen, C_1-C_6alkyl, adamantyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, arylcarbonyl, arylC_1-C_6alkylcarbonyl, C_1-C_6alkylcarboxy or arylC_1-C_6alkylcarboxy wherein the alkyl and aryl groups are optionally substituted; or
R_7 and R_8 are taken together with the nitrogen to which they are attached forming a saturated, partially saturated or aromatic cyclic, bicyclic or tricyclic ring system containing 3 to 14 carbon atoms and from 0 to 3 additional heteroatoms selected from nitrogen, oxygen or sulfur, the ring system can optionally be substituted with at least one C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, hydroxy, oxo, C_1-C_6alkyloxy, arylC_1-C_6alkyloxy, C_1-C_6alkyloxyC_1-C_6alkyl, NR_9R_{10} or C_1-C_6alkylaminoC_1-C_6alkyl, wherein R_9 and R_{10} are independently selected from hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl, C_1-C_6alkylcarbonyl, arylcarbonyl, arylC_1-C_6alkylcarbonyl, C_1-C_6alkylcarboxy or arylC_1-C_6alkylcarboxy; wherein the alkyl and aryl groups are optionally substituted; or
R_7 and R_8 are independently a saturated or partial saturated cyclic 5, 6 or 7 membered amine, imide or lactam;

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

2. A compound according to claim 1 wherein A is furanyl.

3. A compound according to claim 1 wherein A is thiophenyl.

4. A compound according to claim 1 wherein A is pyrrolyl.

5. A compound according to claim 1 wherein A is oxazolyl.

6. A compound according to claim 1 wherein A is thiazolyl.

7. A compound according to claim 1 wherein A is imidazolyl.

8. A compound according to claim 1 wherein A is pyrazolyl.

9. A compound according to claim 1 wherein A is isoxazolyl.

10. A compound according to claim 1 wherein A is isothiazolyl.

11. A compound according to claim 1 wherein A is 1,2,3-oxadiazolyl.

12. A compound according to claim 1 wherein A is furazanyl.

13. A compound according to claim 1 wherein A is 1,2,3-triazolyl.

14. A compound according to claim 2 to 13 wherein R_1 and R_2 are COR_5 and R_4 is hydrogen; wherein R_5 is defined as above.

15. A compound according to claim 2 to 13 wherein R_1 is 5-tetrazolyl and R_2 is COR_5; wherein R_5 is defined as above.

16. A compound according to claim 2 to 13 wherein R_1 and R_2 are COOH and R_4 is hydrogen.

17. A compound selected from the following:

2-Methyl-4-(oxalyl-amino)-1H-pyrrole-3-carboxylic acid;
1-Benzyl-3-(oxalyl-amino)-1H-pyrazole-4-carboxylic acid;

3-(Oxalyl-amino)-1H-pyrazole-4-carboxylic acid;

4-Cyclohexyl-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-4-phenyl-thiophene-3-carboxylic acid;

3-(Oxalyl-amino)-thiophene-2-carboxylic acid;

3-(Oxalyl-amino)-5-phenyl-thiophene-2-carboxylic acid;

4-(Oxalyl-amino)-[2,3]-bithiophenyl-5-carboxylic acid;

4-Methyl-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

2-(Oxalyl-amino)-5-phenyl-thiophene-3-carboxylic acid;

5-(4-Chloro-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(4-Fluoro-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(4-Isobutyl-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

3-(Oxalyl-amino)-5-(4-phenoxy-phenyl)-thiophene-2-carboxylic acid;

5-(4-Benzyloxy-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(4-(4-Methoxy-phenoxy)-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(4-Hydroxy-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(1,3-Dioxo-1,3-dihydro-isoindol-2-ylmethyl)-2-(oxalyl-amino)thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-(phenyl-methyl)thiophene-3-carboxylic acid;

5-(2-(4-Chloro-phenyl)-ethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(Naphthalen-2-yl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3-Nitro-phenyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(2-Fluoro-phenyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3-Chloro-phenyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(2,4-Dichloro-phenyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(4-Bromo-phenyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-Ethyl-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-Methyl-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3-Methyl-phenyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-Dibenzofuran-2-yl-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3,4-Dimethoxy-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(3-Methoxy-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(3,5-Dimethoxy-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(3-Nitro-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(3-Amino-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(4-Methoxy-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(4-(2-(2-Methoxy-phenyl)-2-oxo-ethoxy)-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(4-Carboxymethoxy-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(4-(4-Fluoro-benzyloxy)-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(4-Amino-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-(4-Carbamoylmethoxy-phenyl)-3-(oxalyl-amino)-thiophene-2-carboxylic acid;

5-((2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-acetylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3-Ethoxycarbonylmethyl-ureidomethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3-tert-Butyl-ureidomethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-((3-Ethyl-ureido)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3-(2-Nitro-phenyl)-ureidomethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3-(3-Methoxy-phenyl)-ureidomethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3-(3-Acetyl-phenyl)-ureidomethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-((3-propyl-ureido)-methyl)-thiophene-3-carboxylic acid;

5-(3-(3-Bromo-phenyl)-ureidomethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3-(2,6-Diisopropyl-phenyl)-ureidomethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3-(4-Nitro-phenyl)-ureidomethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-((3-Naphthalen-1-yl-ureido)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-((3-Biphenyl-2-yl-ureido)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3-(3,5-Bis-trifluoromethyl-phenyl)-ureidomethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-(3-(2-trifluoromethyl-phenyl)-ureidomethyl)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-(3-(3-trifluoromethyl-phenyl)-ureidomethyl)-thiophene-3-carboxylic acid;

5-(3-Isopropyl-ureidomethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-((3-Cyclohexyl-ureido)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3-(2-Methoxy-phenyl)-ureidomethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3-Benzyl-ureidomethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(3-(2,4-Dimethoxy-phenyl)-ureidomethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-((3-Adamantan-1-yl-ureido)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-((3-phenyl-ureido)-methyl)-thiophene-3-carboxylic acid;

5-(3-(3-Nitro-phenyl)-ureidomethyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-(3-(3,4,5-trimethoxy-phenyl)-ureidomethyl)-thiophene-3-carboxylic acid;

2-Oxalyl-amino-5-(3-(phenylsulfonyl)ureidomethyl)-thiophene-3-carboxylic acid;

2-Oxalyl-amino-5-(3-(2-methyl-phenylsulfonyl)ureidomethyl)-thiophene-3-carboxylic acid;

2-Oxalyl-amino-5-(3-(4-chloro-phenylsulfonyl)ureidomethyl)-thiophene-3-carboxylic acid;

5-((4-Bromo-phenoxycarbonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-((4-Fluoro-phenoxycarbonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-((2,2-Dimethyl-propoxycarbonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-((2-Nitro-phenoxycarbonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

2-Oxalyl-amino-5-(3-(4-methyl-phenylsulfonyl)ureidomethyl)-thiophene-3-carboxylic acid;

5-((2-Ethyl-hexyloxycarbonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(Benzyloxycarbonylamino-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-(propoxycarbonylamino-methyl)-thiophene-3-carboxylic acid;

5-(Isopropoxycarbonylamino-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-((4-Nitro-phenoxycarbonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-((4-Nitro-benzyloxycarbonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-((4-Methoxy-phenoxycarbonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(Octyloxycarbonylamino-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-(prop-2-ynyloxycarbonylamino-methyl)-thiophene-3-carboxylic acid;

5-(Ethoxycarbonylamino-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(Isobutoxycarbonylamino-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(Allyloxycarbonylamino-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(But-3-enyloxycarbonylamino-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-((4-Bromo-benzenesulfonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(Methoxycarbonylamino-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-(phenoxycarbonylamino-methyl)-thiophene-3-carboxylic acid;

5-((2-Nitro-phenylmethanesulfonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-((4-trifluoromethoxy-benzenesulfonylamino)-methyl)-thiophene-3-carboxylic acid;

5-((4-Chloro-benzenesulfonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-((propane-2-sulfonylamino)-methyl)-thiophene-3-carboxylic acid;

5-((4-Fluoro-benzenesulfonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(Methanesulfonylamino-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-((Naphthalene-1-sulfonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-(Ethanesulfonylamino-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-((3-trifluoromethyl-benzenesulfonylamino)-methyl)-thiophene-3-carboxylic acid;

5-((4-Acetylamino-benzenesulfonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-((propane-1-sulfonylamino)-methyl)-thiophene-3-carboxylic acid;

5-(4-(tert-Butyl-benzenesulfonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

5-((2-Nitro-4-trifluoromethyl-benzenesulfonylamino)-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-((2,2,2-trifluoro-ethanesulfonylamino)-methyl)-thiophene-3-carboxylic acid;

2-(Oxalyl-amino)-5-((2-phenyl-ethenesulfonylamino)-methyl)-thiophene-3-carboxylic acid;

5-(Benzenesulfonylamino-methyl)-2-(oxalyl-amino)-thiophene-3-carboxylic acid;

or a pharmaceutically acceptable salt thereof.

18. Compounds according to any one of the preceding claims which acts as inhibitors or modulators of Protein Tyrosine Phosphatases.

19. A pharmaceutical composition comprising a compound according to any of the claim 1 to 17 or a pharmaceutical acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms together with one or more pharmaceutically acceptable carriers or diluents.

20. A pharmaceutical composition suitable for treating type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance or obesity comprising a compound according to any of the claims 1 to 17 or a pharmaceutical acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or

mixture of optical isomers, including a racemic mixture, or any tautomeric forms together with one or more pharmaceutically acceptable carriers or diluents.

21. A pharmaceutical composition suitable for treating immune dysfunctions including autoimmunity, diseases with dysfunctions of the coagulation system, allergic diseases including asthma, osteoporosis, proliferative disorders including cancer and psoriasis, diseases with decreased or increased synthesis or effects of growth hormone, diseases with decreased or increased synthesis of hormones or cytokines that regulate the release of/or response to growth hormone, diseases of the brain including Alzheimer's disease and schizophrenia, and infectious diseases comprising a compound according to any of the claims 1 to 17 or a pharmaceutical acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms together with one or more pharmaceutically acceptable carriers or diluents.

22. The pharmaceutical composition according to claim 19, 20 or 21 in the form of an oral dosage unit or parenteral dosage unit.

23. A pharmaceutical composition according to claim 19, 20 or 21 wherein said compound is administered as a dose in a range from about 0.05 to 1000 mg, preferably from about 0.1 to 500 mg and especially in the range from 50 to 200 mg per day.

24. A compound according to any one of the claims 1 to 17 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms for therapeutical use.

25. A compound according to any one of the claims 1 to 17 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture,

or any tautomeric forms for therapeutical use in the treatment or preventing of type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance or obesity.

26. A compound according to any one of the claims 1 to 17 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms for therapeutical use in the treatment or preventing of immune dysfunctions including autoimmunity, diseases with dysfunctions of the coagulation system, allergic diseases including asthma, osteoporosis, proliferative disorders including cancer and psoriasis, diseases with decreased or increased synthesis or effects of growth hormone, diseases with decreased or increased synthesis of hormones or cytokines that regulate the release of/or response to growth hormone, diseases of the brain including Alzheimer's disease and schizophrenia, and infectious diseases.

27. The use of a compound according to any one of the claims 1 to 17 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms as a medicament.

28. The use of a compound according to any of the claims 1 to 17 for preparing a medicament.

29. The use of a compound according to any one of the claims 1 to 17 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms for the preparation of a medicament suitable for the treatment or preventing of type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance or obesity.

30. The use of a compound according to any one of the claims 1 to 17 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms for the preparation of a medicament suitable for the treatment or preventing of immune dysfunctions including autoimmunity, diseases with dysfunctions of the coagulation system, allergic diseases including asthma, osteoporosis, proliferative disorders including cancer and psoriasis, diseases with decreased or increased synthesis or effects of growth hormone, diseases with decreased or increased synthesis of hormones or cytokines that regulate the release of/or response to growth hormone, diseases of the brain including Alzheimer's disease and schizophrenia, and infectious diseases.

31. A method of treating type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance or obesity comprising administering to a subject in need thereof an effective amount of a compound according to any of the claims 1 to 17 to said subject.

32. A method of treating immune dysfunctions including autoimmunity, diseases with dysfunctions of the coagulation system, allergic diseases including asthma, osteoporosis, proliferative disorders including cancer and psoriasis, diseases with decreased or increased synthesis or effects of growth hormone, diseases with decreased or increased synthesis of hormones or cytokines that regulate the release of/or response to growth hormone, diseases of the brain including Alzheimer's disease and schizophrenia, and infectious diseases comprising administering to a subject in need thereof an effective amount of a compound according to any of the claims 1 to 17 to said subject.

33. A process for the manufacture of a medicament, particular to be used in the treatment or prevention of type I diabetes, type II diabetes, impaired glucose tolerance, insulin resistance or obesity which process comprising bringing a

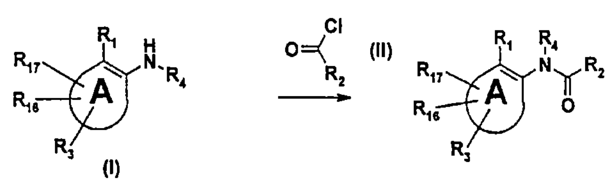
compound according to any of the claims 1 to 17 or a pharmaceutically acceptable salt thereof into a galenic dosage form.

34. A process for the manufacture of a medicament, particular to be used in the treatment or prevention of immune dysfunctions including autoimmunity, diseases with dysfunctions of the coagulation system, allergic diseases including asthma, osteoporosis, proliferative disorders including cancer and psoriasis, diseases with decreased or increased synthesis or effects of growth hormone, diseases with decreased or increased synthesis of hormones or cytokines that regulate the release of/or response to growth hormone, diseases of the brain including Alzheimer's disease and schizophrenia, and infectious diseases which process comprising bringing a compound according to any of the claims 1 to 17 or a pharmaceutically acceptable salt thereof into a galenic dosage form.

35. Any novel feature or combination of features as described herein.

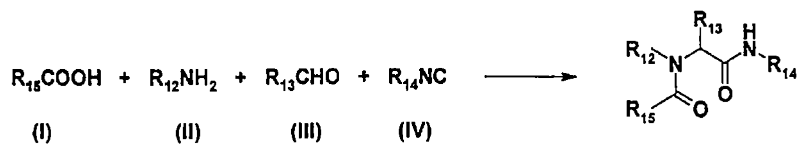
36. A method of preparing a compound of formula 1, characterized in

a)

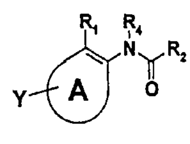


allowing an amino substituted compound of formula (I) to react with an acid chloride of formula (II), wherein A, R_1, R_2, R_3, R_4, R_{16} and R_{17} are defined as above, or

b)



allowing a carboxylic acid (I), a primary amine (II) and an aldehyde (III) to react with a isocyanide (IV) wherein R_{12}, R_{13}, R_{14}, and R_{15} are independently selected from the group consisting of hydrogen, C_1-C_6alkyl, aryl, arylC_1-C_6alkyl as defined above and the alkyl and aryl groups are optionally substituted as defined above; or R_{12}, R_{13}, R_{14}, and R_{15} are independently selected from



wherein Y indicates attachment point for R_{12}, R_{13}, R_{14}, and R_{15} and A, R_1 R_2 and R_4 are defined as above, or

c)

the above described four component Ugi reaction (method b) is carried out by attaching any one of the components to a solid support whereby the synthesis is accomplished in a combinatorial chemistry fashion.

37. Compounds according to claim 1 to 17 which acts as ligands, inhibitors or modulators of molecules with pTyr recognition units including proteins that contain SH2 domains.